Protocol J3V-MC-KKAA(d)

A Phase 1, Multicenter, Randomized, Placebo-Controlled, Double-Blind, Single-Ascending Dose Study of LY3844583 in Healthy Participants, and Multiple-Dose Study of LY3844583 in Healthy Participants and Patients with Atopic Dermatitis

NCT05486208

Approval Date: 08-Jun-2023

Title Page

Confidential Information

The information contained in this document is confidential and is intended for the use of clinical investigators. It is the property of Eli Lilly and Company or its subsidiaries and should not be copied by or distributed to persons not involved in the clinical investigation of GITR Antagonist Antibody (LY3844583) unless such persons are bound by a confidentiality agreement with Eli Lilly and Company or its subsidiaries.

Note to Regulatory Authorities: This document may contain protected personal data and/or commercially confidential information exempt from public disclosure. Eli Lilly and Company requests consultation regarding release/redaction prior to any public release. In the United States, this document is subject to Freedom of Information Act (FOIA) Exemption 4 and may not be reproduced or otherwise disseminated without the written approval of Eli Lilly and Company or its subsidiaries.

Protocol Title:

A Phase 1, Multicenter, Randomized, Placebo-Controlled, Double-Blind, Single-Ascending Dose Study of LY3844583 in Healthy Participants, and Multiple-Dose Study of LY3844583 in Healthy Participants and Patients with Atopic Dermatitis

Protocol Number: J3V-MC-KKAA

Amendment Number: d

Compound: LY3844583

Brief Title: A Single-Ascending Dose Study of LY3844583 in Healthy Participants, and Multiple-Dose Study of LY3844583 in Healthy Participants and Patients with Atopic Dermatitis.

Study Phase: Phase 1

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Eli Lilly and Company, Indianapolis, Indiana USA 46285.

Regulatory Agency Identifier Number(s)

IND: 160550

Approval Date: Protocol Electronically Signed and Approved by Lilly on date provided below.

Document ID: VV-CLIN-118939

Medical Monitor Name and Contact Information will be provided separately.

Approved on 08 Jun 2023 GMT

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment c	*12-May 2023*
Amendment b	*09-February 2023*
Amendment a	*23-January 2023*
Original Protocol	*14-March 2022*

Amendment d

This protocol has been amended to increase the number of enrolled patients with atopic dermatitis in Part C to provide a more precise understanding of the safety, tolerability, pharmacokinetics and pharmacodynamic effects.

Minor editorial changes have also been done and are not presented in the summary of changes table.

Section # and Name	Description of Change	Brief Rationale
Section 1.1: Synopsis	Updated the total number of enrolled participants from approximately CCI to approximately 102. Updated the total number of evaluable participants from approximately CCI to approximately CCI (CCI healthy participants and up to CCI patients with atopic dermatitis). Updated the number of patients with atopic dermatitis enrolled in Part C from CCI to up to CCI	Up to an additional CCI participants were added to Part C to provide more precise understanding of the safety, tolerability, pharmacokinetics and pharmacodynamic effects in patients. This increases the total number of enrolled and evaluable participants.
CCI [redacted]	[redacted]	[redacted]

Section # and Name	Description of Change	Brief Rationale
Section 4.1: Overall Design	Updated the number of patients with atopic dermatitis in Part C from [redacted] to up to [redacted] Updated the number of patients with atopic dermatitis to receive LY3844583 from [redacted] to [redacted] and updated the number of patients with atopic dermatitis to receive placebo from [redacted] to [redacted] Updated the ratio for Repeat-dose Part C in Table KKAA.1 from [redacted] LY:[redacted] PBO to [redacted] LY:[redacted] PBO Added footnote b to Table KKAA.1 to the dosing ratio to clarify that the allocation ratio is [redacted]LY:[redacted]PBO. The stated ratio is only observed if [redacted] patients are enrolled. Added footnote c to Table KKAA.1 to the number of planned completers for Part C to clarify that [redacted] is the minimum number of completers.	Up to an additional [redacted] participants were added to Part C to provide more precise understanding of the safety, tolerability, pharmacokinetics and pharmacodynamic effects in patients. This increases the total number of enrolled and evaluable participants and the number of patients with atopic dermatitis. Provide clarity on the minimum number of planned completers in Part C.
Section 9.5: Sample Size Determination	Updated the total number of enrolled participants from approximately [redacted] to approximately [redacted] ([redacted] healthy participants and up to [redacted] patients with atopic dermatitis).	Up to an additional [redacted] participants were added to Part C to provide more precise understanding of the safety, tolerability, pharmacokinetics and pharmacodynamic effects in patients. This increases the total number of evaluable participants.

Table of Contents

1. Protocol Summary 10
1.1. Synopsis 10
CCI [redacted]
1.3. Schedule of Activities (SoA) 14
1.3.1. Part A: Single-ascending Dose in Healthy Participants 14
1.3.2. Part B: Multiple-ascending Dose in Healthy Participants 18
1.3.3. Part C: Repeat Dose in Patients with Atopic Dermatitis 28

2. Introduction 37
2.1. Study Rationale 37
2.2. Background 37
2.3. Benefit/Risk Assessment 39

3. Objectives, Endpoints, and Estimands 41

4. Study Design 43
4.1. Overall Design 43
4.2. Scientific Rationale for Study Design 46
4.3. Justification for Dose 47
4.4. End of Study Definition 53

5. Study Population 54
5.1. Inclusion Criteria 54
5.1.1. Additional Inclusion Criteria for Part C (Patients with AtD) 55
5.2. Exclusion Criteria 56
5.2.1. Additional Exclusion Criteria for Part C (Patients with AtD) 59
5.3. Lifestyle Considerations 60
5.3.1. Meals and Dietary Restrictions 60
5.3.2. Substance Use: Caffeine, Alcohol, and Tobacco 61
5.4. Screen Failures 61
5.5. Criteria for Temporarily Delaying Enrollment/Randomization/ Administration of Study Intervention of a Participant 62

6. Study Intervention(s) and Concomitant Therapy 63
6.1. Study Intervention(s) Administered 63
6.1.1. Administration Details 63
6.1.2. Premedication for Infusions 63
6.1.3. Management of Infusion Reactions 64
6.2. Preparation, Handling, Storage, and Accountability 65
6.3. Measures to Minimize Bias: Randomization and Blinding 65
6.4. Study Intervention Compliance 66
6.5. Dose Modification 66
6.5.1. Dose Decision/Escalation 67
6.6. Continued Access to Study Intervention after the End of the Study 69
6.7. Treatment of Overdose 69
6.8. Concomitant Therapy 69

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal....72
7.1. Discontinuation of Study Intervention....72
7.1.1. Rules for Stopping Dosing and Enrollment in a Cohort....72
7.1.2. Liver Chemistry Stopping Criteria....72
7.1.3. Discontinuation related to Hepatitis B Virus....73
7.1.4. Participant Discontinuation/Withdrawal from the Study....73
7.1.5. Discontinuation of Inadvertently Enrolled Participants....74
7.2. Lost to Follow-up....74

8. Study Assessments and Procedures....75
8.1. Efficacy Assessments....75
8.2. Safety Assessments....76
8.2.1. Physical Examinations....77
8.2.2. Vital Signs....77
8.2.3. Electrocardiograms....77
8.2.4. Clinical Safety Laboratory Tests....78
8.2.5. Injection-site Reactions....79
8.2.6. Safety Monitoring....80
8.2.7. Immunological Status Assessments....81
8.2.8. Hepatitis B Testing and Monitoring....81
8.2.9. Hepatitis C Testing....81
8.2.10. Pregnancy Testing....81
8.3. Adverse Events, Serious Adverse Events, and Product Complaints....82
8.3.1. Timing and Mechanism for Collecting Events....84
8.3.2. Pregnancy....85
8.3.3. Adverse Events of Special Interest....86
8.4. Pharmacokinetics....86
8.4.1. Bioanalytics....87
8.5. Pharmacodynamics....87
8.6. Genetics....87
8.7. Biomarkers....88
8.7.1. Skin Biopsies for Participants with Atopic Dermatitis....88
8.8. Immunogenicity Assessments....89
8.9. Health Economics or Medical Resource Utilization and Health Economics....89

9. Statistical Considerations....90
9.1. Statistical Hypotheses....90
9.1.1. Multiplicity Adjustment....90
9.2. Populations for Analyses....90
9.2.1. Study Participant Disposition....90
9.2.2. Study Participant Characteristics....91
9.2.3. Treatment Compliance....91
9.3. Statistical Analyses....91
9.3.1. General Considerations....91
9.3.2. Primary Endpoint....91

9.3.3. Pharmacokinetic Analyses 92
9.3.4. Exploratory Endpoints 92
CCI [redacted]
9.4. Interim Analysis 95
9.5. Sample Size Determination 95

10. Supporting Documentation and Operational Considerations 97
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 97
10.1.1. Regulatory and Ethical Considerations 97
10.1.2. Informed Consent Process 97
10.1.3. Data Protection 98
10.1.4. Committees Structure 98
10.1.5. Dissemination of Clinical Study Data 98
10.1.6. Data Quality Assurance 99
10.1.7. Source Documents 100
10.1.8. Study and Site Start and Closure 101
10.1.9. Publication Policy 101
10.2. Appendix 2: Clinical Laboratory Tests 102
10.2.1. Blood Sampling Summary 105
10.3. Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 110
10.3.1. Definition of AE 110
10.3.2. Definition of SAE 111
10.3.3. Definition of Product Complaints 112
10.3.4. Recording and Follow-up of AE and/or SAE and Product Complaints 112
10.3.5. Reporting of SAEs 114
10.3.6. Regulatory Reporting Requirements 114
10.4. Appendix 4: Contraceptive and Barrier Guidance 116
10.4.1. Definitions 116
10.4.2. Contraception Guidance 117
10.5. Appendix 5: Genetics 119
10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments and Study Intervention Restart/Rechallenge Guidelines 121
10.6.1. Hepatic Monitoring and Abnormal Hepatic Biochemical Tests 121
10.7. Appendix 7: Abbreviations and Definition 125
10.8. Appendix 8: Protocol Amendment History 130

11. References 138

Table of Contents

Table **Page**

Table KKAA.1. Summary of Participant Cohorts 45

Table KKAA.2. NOAEL-based Dose and Model-predicted Exposure Multiples for Proposed Single and Repeated Administrations of LY3844583 to Human Participants 50

Table KKAA.3. Predicted PK/PD and Exposure Multiples to NOAEL Doses for Planned SAD Doses with Scaling of Vmax 51

Table KKAA.4. Predicted PK/PD and Exposure Multiples to NOAEL Doses for Planned SAD Doses without Scaling of Vmax 52

Table of Contents

Figure **Page**

Figure KKAA.1. Study schema. 13

Approved on 08 Jun 2023 GMT

1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Phase 1, Multicenter, Randomized, Placebo-Controlled, Double-Blind, Single-Ascending Dose Study of LY3844583 in Healthy Participants, and Multiple-Dose Study of LY3844583 in Healthy Participants and Patients with Atopic Dermatitis

Brief Title: A Single-Ascending Dose Study of LY3844583 in Healthy Participants, and Multiple-Dose Study of LY3844583 in Healthy Participants and Patients with Atopic Dermatitis.

Regulatory Agency Identifier Number: IND: 160550

Rationale:

Study J3V-MC-KKAA (KKAA) is the first-in-human dose study that will investigate the safety, tolerability, and pharmacokinetics (PK) of single- and multiple-ascending doses of LY3844583 in healthy participants and patients with atopic dermatitis (AtD). The data generated in this study will guide the design of subsequent clinical trials.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
To assess the safety and tolerability of LY3844583 after single- and multiple-dose administrations in healthy participants and after repeat-dose administration in the participants with AtD.	Incidence of AEs, TEAEs, and SAEs
Secondary	
To characterize the PK of LY3844583 following single- and multiple-dose administrations in healthy participants and after repeat dosing in participants with AtD.	C_{max} and AUC

Abbreviations: AE = adverse event; AtD = atopic dermatitis; AUC = area under the concentration versus time curve; C_{max} = maximum observed drug concentration; PK = pharmacokinetics; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Estimands:

Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) will be listed and, if the frequency of events allows, descriptive statistics will summarize the safety data per race and ethnicity. Symptoms, their incidence, severity, and association with investigational product, as perceived by the investigator, will be reported separately for each treatment. All TEAEs will be summarized across each part of the study by system organ class and by decreasing frequency according to the Medical Dictionary for Regulatory Activities.

Overall Design:

Study KKAA is a first-in-human trial designed to evaluate safety, tolerability, PK of LY3844583 in healthy participants and participants with AtD. The inclusion of healthy Japanese and Chinese participants in this study will facilitate the inclusion of Japanese and Chinese participants in subsequent clinical trials. The study will be conducted in 3 parts as follows:

- Part A (single-ascending dose [SAD]) will assess the safety, tolerability, PK, and CCI of single subcutaneous (SC) and intravenous (IV) doses of LY3844583 in healthy participants.
- Part B (multiple-ascending dose [MAD]) will assess the safety, tolerability, PK, and CCI of multiple SC and/or IV doses of LY3844583 in healthy participants.
- Part C (repeat dose) will assess the safety, tolerability, PK, CCI and exploratory data of multiple SC or IV doses of LY3844583 in patients with AtD.

Brief Summary:

This is a randomized, placebo-controlled, sequential design, sponsor-unblinded, investigator- and participant-blinded SAD and MAD study in healthy participants and randomized, placebo-controlled, double blinded, repeat-dose study in patients with AtD.

Study details include:

- Treatment duration
  - Part A - Single-dose administration for each healthy participant.
  - Part B - CCI days of treatment period; up to CCI doses at an interval of CCI for each healthy participant.
  - Part C - Up to CCI weeks treatment period; up to CCI doses administered at an interval of CCI for each patient with AtD.
- Visit frequency
  - Part A - Inpatient for approximately CCI days followed by visits at regular intervals.
  - Part B - Inpatient following each dosing and discharge at the discretion of the investigator, visits in between the doses and at regular intervals following the last dose of the study drug.
  - Part C - Each dosing and discharge at the discretion of the investigator, visits in between the doses and at regular intervals following the last dose of the study drug.

Number of Participants:

Approximately 102 participants in total (healthy participants and patients with AtD) may be enrolled to ensure that approximately CCI evaluable participants (CCI healthy participants and up to CCI patients with AtD) complete the study. Participants will include:

- CCI healthy participants in the SAD Part A
  - up to an additional CCI healthy participants may be enrolled in optional SAD cohorts.
- CCI healthy participants in the MAD Part B, and
- CCI patients with AtD in Part C.

Intervention Groups and Duration:

SAD Part A

A total of 3 SC dose cohorts (CCI CCI and CCI mg) and 2 IV dose cohorts (CCI and CCI mg) are planned. Optional Cohorts 6 and 7 may be enrolled depending on emerging data from earlier cohorts. Study intervention will be administered as a single dose on Day CCI followed by a CCI week follow-up period.

MAD Part B

At least 2 IV or SC dose cohorts (CCI mg Cohort 1 and ≤CCI mg Cohort 2) are planned. Study intervention is planned to be administered to healthy participants via the IV route CCI on Days CCI in Cohort 1, and via either IV or SC route CCI on Days CCI in Cohort 2. The route and frequency of administration will be confirmed based on emerging data from SAD cohorts. Participants will be followed up for CCI weeks after the last dose.

Repeat-dose Part C

At least 1 IV or SC dose cohort (≤CCI mg) is planned. Study intervention will be administered on Day CCI followed by dose administration CCI or CCI for CCI weeks in patients with AtD. The route and frequency will be confirmed based on emerging data from SAD Part A and MAD Part B cohorts. Participants will be followed up for CCI weeks after the last dose.

In all parts of the study, treatment-matched placebo will be given using the same time, frequency, and route as LY3844583, as applicable.

Ethical Considerations of Benefit/Risk: Not applicable

Data Monitoring Committee: No



Approved on 08 Jun 2023 GMT

1.3. Schedule of Activities (SoA)

1.3.1. Part A: Single-ascending Dose in Healthy Participants

Procedures/Assessments	Screening	Treatment Period								Follow-up								ED
Visit Number	V1	V2								V3	V4	V5	V6	V7	V8	V9	V10	
Study Day	CCI																	
Review/confirm I/E criteria	X	X[a]																
Informed consent	X																	
Admission to CRU[b]		X																
Randomization			X															
Discharge from CRU[b]									X									
Outpatient visit										X	X	X	X	X	X	X	X	X
Clinical Assessments																		
Complete medical history	X																	
Review preexisting conditions/AEs	X	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Substance use (alcohol and tobacco use)[c]	X	X											X				X	X
Physical examination[d]	X	X															X	X
Weight	X	X															X	X
Height	X																	
Vital signs (pulse rate, blood pressure, and temperature)[e,f]	X	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECGs[f,g]	X		X	X	X		X		X		X		X		X		X	X

Procedures/Assessments	Screening	Treatment Period								Follow-up								ED
Visit Number	V1	V2								V3	V4	V5	V6	V7	V8	V9	V10	
Study Day	CCI																	
Chest x-ray[h] (posterior-anterior view)	X																	
QuantiFERON®-TB Gold test or TST[i]	X																	
IP administration	CCI																	
Laboratory Assessments																		
Serologies (Hepatitis B, Hepatitis C, HIV)	X																	
Serum immunoglobulins[j]	CCI																	
Subcutaneous local injection-site assessment[l]																		
Urinary drug screen	X	X																
FSH[m]	X																	
Pregnancy test[m]	X	X															X	X
Clinical chemistry	X	X		X	X		X		X		X	X	X	X	X	X	X	X
Hematology	X	X		X	X		X		X		X	X	X	X	X	X	X	X
Urinalysis	X	X		X	X		X		X		X		X	X			X	X
Pharmacogenetics		X																
Immunogenicity[n]	CCI																	
Blood samples for flow cytometry (safety)[o]																		

CCI

Procedures/Assessments	Screening	Treatment Period							Follow-up								ED
Visit Number	V1	V2							V3	V4	V5	V6	V7	V8	V9	V10	
Study Day	CCI																
CCI																	
T-Regulator Proliferation Panel 2[t]			predose[k]						X			X				X	X

Abbreviations: AE = adverse event; CRU = clinical research unit; CT = computed tomography; CXR = chest x-ray; CCI; ECG = electrocardiogram; ED = early discontinuation; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; I/E = inclusion/exclusion; Ig = immunoglobulin; IP = investigational product; IV = intravenous; PK = pharmacokinetic; CCI; SC = subcutaneous; TB = tuberculosis; Treg = regulatory T cell; TST = tuberculin skin test; V = visit.

[a] At the discretion of the clinical site, the baseline measurement for this assessment can be collected at any time prior to dosing on the day of dosing.

[b] Admission to the CRU may occur on the day prior to dosing or during morning of the day of dosing at the discretion of the CRU, and discharge from the CRU can occur following completion of the Day CCI assessments.

[c] Unscheduled testing is allowed.

[d] Full physical examination at screening, CCI days and ED. At admission, medical assessment only performed to include medical review and a brief physical exam examination. Symptom-directed physical examinations may be conducted at any time during the study, as deemed necessary by the investigator.

[e] On Day CCI blood pressure and pulse rate will be assessed at predose, end of infusion (for IV only), 3-, 6-, 12-hour postdose. Temperature measurement is required only at screening and baseline.

[f] On days with concurrent ECG, vital sign, and/or PK sampling, these measurements should occur at approximately the same time. ECG recording and vital sign measurements should occur prior to the blood draw. A single ECG will be obtained at screening and Day CCI but not transmitted to the central ECG vendor (Section 8.2.3). At all other time points, consecutive ECGs are to be obtained in triplicate at approximately 1-min intervals. Additional tracings may be taken at each time point to obtain high quality data, when needed.

[g] Times are referenced to end of dosing. ECGs will be obtained on Day CCI (predose [any time prior to dosing on the day of dosing but within approximately 90 minutes prior to the predose blood draw], end of infusion, and approximately 6 hours after the end of infusion for the IV cohort and predose only for the SC cohort), Day CCI (approximately 24 hours after the end of dosing for both the IV and SC cohorts), and at any time on other specified visits (but prior to any blood draws at same visit).

[h] A posterior-anterior CXR will be performed at screening unless one has been performed within the past 6 months and the x-ray and reports are available. Note: Results of a chest CT scan or other imaging study similar to a CXR may be substituted in place of the CXR as described above, in consultation with the sponsor's medical monitor.

[i] The follow-up TST reading should occur CCI days after screening.

[j] Includes IgA, IgM, IgD, IgE, and IgG: to be done centrally.

[k] This activity should be completed any time before IP administration (predose).

[l] Injection-site assessments will be performed at the indicated time points on each study day. If injection-site reactions (ISRs) either persist or appear at any time point up to Study Day [redacted] injection-site assessment can be repeated until resolution. These additional assessments should be conducted at the CRU on days participants are scheduled for outpatient activities (for example, on days PK, exploratory samples, and [redacted] samples are collected). Findings to be reported using the Injection Site Reaction Observational form. [redacted]. Pain VAS to be administered if participant reports pain in the injection-site reaction observational form. See Section 8.2.5.1 for further details.

[m] A serum pregnancy test will be conducted at screening only. For women who are considered to be not of childbearing potential, FSH should be drawn to confirm status as defined in inclusion criteria.

[n] In the event of drug hypersensitivity reactions (immediate or nonimmediate), up to 3 additional samples will be collected each for PK and immunogenicity at the following time points: as close to the onset of the reaction event as possible, at the resolution of the event if possible, and approximately 30 days following the event.

[o] Can be performed centrally and/or locally.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[t] Failure to collect at the planned time points will not result in a protocol deviation.

1.3.2. Part B: Multiple-ascending Dose in Healthy Participants

1.3.2.1. Part B: Cohort 1 – CCI Dosing Schedule

Procedures/ Assessments	Screening	Treatment Period																		Follow-up						ED
Visit Number	V1	V2					V3	V4	V5					V6	V7					V8	V9	V 10	V 11	V 12	V 13	
Study Day(s)	CCI																									
Review/confirm I/E criteria	X	X[b]																								
Informed consent	X																									
Admission to CRU[c]		X							X						X											
Randomization			X																							
Discharge from CRU[c]							X						X						X							
Outpatient visit								X	X					X						X	X	X	X	X	X	
Clinical Assessments																										
Complete medical history	X																								X	X
Review preexisting conditions/AEs	X	X[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X[b]	X	X	X	X	X	X	X	X	X	X[b]	X	X	X[b]	X	X		X	X	X	X	X	X	X	X	X
Substance use (alcohol, tobacco use)[d]	X	X							X						X							X				X
Physical examination[e]	X	X	X								X			X											X	X
Weight	X	X																							X	X
Height	X																									

Procedures/ Assessments	Screening	Treatment Period															Follow-up						ED
Visit Number	**V1**	**V2**					**V3**	**V4**		**V5**				**V6**		**V7**					**V8**	**V9**	**V 10**	**V 11**	**V 12**	**V 13**	
Study Day(s)	CCI																										
Vital signs (heart rate, blood pressure, and temperature)[f,g]	X	X	X[b]	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECGs[g,h]	CCI																										
Chest x-ray[j] (posterior-anterior view)	X																										
IP administration	CCI																										
QuantiFERON® -TB Gold test or TST[k]	X																										
Laboratory Assessments[l]																											
Serologies (Hepatitis B, Hepatitis C, HIV)	X																										
Serum immuno globulins[m]	CCI																										
Subcutaneous local injection-site assessment[n]																											

Procedures/ Assessments	Screening	Treatment Period																Follow-up						ED
Visit Number	V1	V2					V3	V4	V5					V6	V7			V8	V9	V 10	V 11	V 12	V 13	
Study Day(s)	CCI																							
Urinary drug screen[d]	X	X							X						X									
FSH[o]	X																							
Pregnancy test[o]	X	X						X							X								X	X
Clinical chemistry	CCI																							
Hematology																								
Urinalysis																								
Pharmacogenetics		X																						
Immunogenicity[p]	CCI																							
Blood samples for flow cytometry (safety)[q]	CCI																							
	CCI																							
T-regulator proliferation panel 2[u]	CCI																							

Abbreviations: AE = adverse event; CRU = clinical research unit; CCI ECG = electrocardiogram; ED = early discontinuation; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; I/E = inclusion/exclusion; Ig = immunoglobulin; IP = investigational product; IV = intravenous; PK = pharmacokinetic; CCI ; TB = tuberculosis; TST = tuberculin skin test; V = visit.

Note: Missed CCI sample collection will not be considered a protocol deviation.

[a] Sample collection window in relation to 0-hour study intervention administration Days CCI

[b] At the discretion of the clinical site, the baseline measurement for this assessment can be collected at any time prior to dosing on the day of dosing.

[c] Admission to the CRU may occur on the day prior to dosing or during morning of the day of dosing at the discretion of the CRU, and discharge from the CRU can occur following completion of the assessments at the discretion of the investigator.

[d] Unscheduled testing is allowed.

[e] Symptom-directed physical examinations may be conducted at any time during the study, as deemed necessary by the investigator.

[f] On IP dosing days, blood pressure and pulse rate will be assessed at predose, end of infusion (for IV only), 3-, 6-, 12-hour postdose. Temperature measurement is required only at screening and baseline.

[g] ECGs should be obtained up to 10 minutes before the scheduled blood draw, and after the participant has been supine for at least 5 minutes and remain supine but awake during ECG collection. A single ECG will be obtained at screening and Day CCI but not transmitted to the central ECG vendor.

[h] Times are referenced to end of dosing unless indicated otherwise.

[i] This activity should be completed any time before IP administration (predose).

[j] A posterior-anterior chest x-ray will be performed at screening unless one has been performed within the past 6 months and the x-ray and reports are available. Note: Results of a chest CT scan or other imaging study similar to a CXR may be substituted in place of the CXR as described above, in consultation with the Lilly's Clinical Pharmacologist.

[k] The follow-up TST reading should occur CCI after screening.

[l] CCI

[m] Includes IgA, IgM, IgD, IgE, and IgG: to be done centrally. However, if results from central testing are delayed, then assessments can be done locally.

[n] Injection-site assessments will be performed at the indicated time points on each study day for SC administration. If injection-site reactions (ISRs) persist at CCI days following injection, injection-site assessment to be repeated until resolution. These additional assessments should be conducted at the CRU on days participants are scheduled for outpatient activities (for example, on days PK, exploratory, and CCI samples are collected). Findings to be reported using the Injection Site Reaction Observational form. CCI . Pain VAS to be administered if participant reports pain in the injection-site reaction observational form. See Section 8.2.5.1 for further details.

[o] A serum pregnancy test will be conducted at screening only. For women who are considered to be not of childbearing potential, FSH should be drawn to confirm status as defined in inclusion criteria.

[p] In the event of drug hypersensitivity reactions (immediate or nonimmediate), up to 3 additional samples will be collected each for PK and immunogenicity as close to the onset of the reaction event as possible, at the resolution of the event if possible, and 30 days following the event.

[q] Can be performed centrally and/or locally.

[r] CCI

[s] CCI

[redacted]

[redacted]

[u] Failure to collect at the planned time points will not result in a protocol deviation.

1.3.2.2. Part B: Cohort 2 – CCI Dosing Schedule

Procedures/ Assessments	Screening	Treatment Period																Follow-Up									ED
Visit Number	V1	V2		V3	V4	V5		V6		V7	V8		V9			V10	V11	V12	V13	V14	V15	V16	V17	V18		
Study Day(s)	CCI																										
Review/confirm I/E criteria	X	X[b]																									
Informed consent	X																										
Admission to CRU[c]		X					X			X				X			X										
Randomization			X																								
Discharge from CRU[c]				X					X			X				X			X								
Outpatient visit					X	X							X							X	X	X	X	X	X	X	X	
Clinical Assessments																												
Complete medical history	X																									X	X
Review preexisting conditions/AEs	X	X	X[b]	X	X	X	X	X[b]	X	X	X[b]	X	X	X	X[b]	X	X	X[b]	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X[b]	X	X	X	X	X[b]	X	X	X[b]	X[b]	X	X	X[b]	X	X	X[b]	X	X	X	X	X	X	X	X	X	X
Substance use (alcohol, tobacco use)[d]	X	X					X			X				X			X						X				X
Physical examination[e]	X	X	X															X						X	X		X	X
Weight	X	X																									X	X
Height	X																											
Vital signs (heart rate, blood pressure, and temperature)[f,g]	X	X	X[b]	X	X	X	X	X[b]	X	X	X[b]	X	X	X	X[b]	X	X	X[b]	X	X	X	X	X	X	X	X	X	X

Procedures/ Assessments	Screening	Treatment Period								Follow-Up								ED
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	
Study Day(s)	CCI																		
ECGs[g,h]	CCI																		
Chest x-ray[j] (posterior-anterior view)	X																		
IP administration	CCI																		
QuantiFERON® -TB Gold test or TST[k]	X																		
Laboratory Assessments[l]																			
Serologies (Hepatitis B, Hepatitis C, HIV)	X																		
Serum immuno-globulins[m]	CCI																		

Procedures/ Assessments	Screening	Treatment Period														Follow-Up										ED
Visit Number	**V1**	**V2**		**V3**	**V4**	**V5**			**V6**		**V7**	**V8**			**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**		
Study Day(s)	CCI																									
Subcutaneous local injection-site assessment[n]																										
Urinary drug screen[d]	X	X					X			X				X			X										
FSH[o]	X																									
Pregnancy test[o]	X	X					X			X				X			X								X	X
Clinical chemistry	CCI																									
Hematology																										
Urinalysis																										
Pharmaco-genetics		X																								
Immuno-genicity[p]	CCI																									
Blood samples for flow cytometry (safety)[q]																										

Procedures/ Assessments	Screening	Treatment Period								Follow-Up									ED
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	
Study Day(s)	CCI																		
proliferation panel 2[u]	CCI																		

Abbreviations: AE = adverse event; CRU = clinical research unit; CT = computed tomography; CXR = chest x-ray; CCI; ECG = electrocardiogram; ED = early discontinuation; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; I/E = inclusion/exclusion; Ig = immunoglobulin; IP = investigational product; ISR = injection site reaction; IV = intravenous; PK = pharmacokinetic; CCI; SC = subcutaneous; TB = tuberculosis; TST = tuberculin skin test; V = visit; VAS = visual analog scale.

Notes: Visits 3, 7, and 10 are required for subcutaneous dosing groups only. Missed CCI sample collection will not be considered a protocol deviation.

[a] Sample collection window in relation to 0-hour study intervention administration Days CCI

[b] At the discretion of the clinical site, the baseline measurement for this assessment can be collected at any time prior to dosing on the day of dosing.

[c] Admission to the CRU may occur on the day prior to dosing or during morning of the day of dosing at the discretion of the CRU, and discharge from the CRU can occur following completion of the assessments at the discretion of the investigator.

[d] Unscheduled testing is allowed.

[e] Symptom-directed physical examinations may be conducted at any time during the study, as deemed necessary by the investigator.

[f] On IP dosing days, blood pressure and pulse rate will be assessed at predose, end of infusion (for IV only), 3-, 6-, 12-hour postdose. Temperature measurement is required only at screening and baseline.

[g] ECGs should be obtained up to 10 minutes before the scheduled blood draw, and after the participant has been supine for at least 5 minutes and remain supine but awake during ECG collection. A single ECG will be obtained at screening and Day CCI but not transmitted to the central ECG vendor.

[h] Times are referenced to end of dosing unless indicated otherwise.

[i] This activity should be completed any time before IP administration (predose).

j A posterior-anterior chest x-ray will be performed at screening unless one has been performed within the past 6 months and the x-ray and reports are available. Note: Results of a chest CT scan or other imaging study similar to a CXR may be substituted in place of the CXR as described above, in consultation with the Lilly's Clinical Pharmacologist.

k The follow-up TST reading should occur CCI days after screening.

CCI [redacted]

m Includes IgA, IgM, IgD, IgE, and IgG: to be done centrally. However, if results from central testing are delayed, then assessments can be done locally.

n Injection-site assessments will be performed at the indicated time points on each study day for SC administration only. If injection-site reactions (ISRs) persist at CCI following injection, injection-site assessment to be repeated until resolution. These additional assessments should be conducted at the CRU on days participants are scheduled for outpatient activities (for example, on days PK, exploratory, and CCI samples are collected). Findings to be reported using the ISR Observational form. CCI [redacted]. Pain VAS to be administered if participant reports pain in the injection-site reaction observational form. See Section 8.2.5.1 for further details.

o A serum pregnancy test will be conducted at screening only. For women who are considered to be not of childbearing potential, FSH should be drawn to confirm status as defined in inclusion criteria.

CCI [redacted]

q Can be performed centrally and/or locally.

CCI [redacted]

CCI [redacted]

CCI [redacted]

u Failure to collect at the planned time points will not result in a protocol deviation.

1.3.3. Part C: Repeat Dose in Patients with Atopic Dermatitis

1.3.3.1. Part C: CCI Dosing Schedule

Procedures/ Assessments	Screening	Treatment Period									Follow-up				ED
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	
Study Day(s)	CCI														
Review/confirm I/E criteria	X	X													
Informed Consent	X														
Complete medical history	X														
Review preexisting conditions/AEs	X	X[a]	X	X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X	X	X	X	X
Concomitant medications	X	X[a]	X	X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X	X	X	X	X
Previous and current AtD treatments	X														
Substance use (alcohol, tobacco use)	X														
Physical examination[b]	X													X	X
Weight	X													X	X
Height	X														
Vital signs (heart rate, blood pressure, and temperature)[c,d]	X	X[a]	X	X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X	X	X	X	X
ECGs[d,e]	X	X			X	X								X	X
Chest x-ray[f] (posterior-anterior view)	X														
IP administration	CCI														
QuantiFERON®-TB Gold test or TST[g]	X														

Procedures/ Assessments	**Screening**	**Treatment Period**									**Follow-up**				**ED**
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	
Study Day(s)	CCI														
vIGA-AD	X	X		X	X	X	X	X	X	X		X	X	X	X
EASI	X	X		X	X	X	X	X	X	X		X	X	X	X
SCORAD	X	X		X	X	X	X	X	X	X		X	X	X	X
POEM[h]	X	X		X	X	X	X	X	X	X		X	X	X	X
DLQI[h]	X	X		X	X	X	X	X	X	X		X	X	X	X
Itch numeric rating scale (NRS)[h]	X	X		X	X	X	X	X	X	X		X	X	X	X
Beta-D-glucan[i]	X														
Serologies (hepatitis B, hepatitis C, HIV) and syphilis testing	X														
Serum immunoglobulins[j]	X					X		X		X				X	X
Urinary drug screen	X														
FSH[k]	X														
Pregnancy test[k]	X	X			X	X	X	X	X	X				X	X
Clinical chemistry	X	X		X	X	X		X		X		X	X	X	X
Hematology	X	X		X	X	X		X		X		X	X	X	X
Urinalysis	X	X		X	X	X		X		X		X	X	X	X
Pharmacogenetics	CCI														
Immunogenicity[l]															
Blood samples for flow cytometry (safety)															

Approved on 08 Jun 2023 GMT

Procedures/ Assessments	Screening	Treatment Period									Follow-up				ED
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	
Study Day(s)	CCI														
CCI															
CCI															
Skin biopsies: nonlesional and lesional[s]		X								X					
CCI															
T-regulator proliferation panel 2[t]	CCI														

Abbreviations: AE = adverse event; AtD= atopic dermatitis; CT = computed tomography; CXR = chest x-ray; CCI; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; ED = early discontinuation; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; I/E = inclusion/exclusion; Ig = immunoglobulin; IP = investigational product; IV = intravenous; NRS = numeric rating scale; PK = pharmacokinetic; POEM = Patient-Oriented Eczema Measure; SCORAD = SCORing Atopic Dermatitis; TB = tuberculosis; TST = tuberculin skin test; V = visit; vIGA-AD = Validated Investigator's Global Assessment for Atopic Dermatitis.

Note: Missed CCI sample collection will not be considered a protocol deviation.

[a] At the discretion of the clinical site, the baseline measurement for this assessment can be collected at any time prior to dosing on the day of dosing.

[b] Full physical examination at screening, Day CCI and ED. Symptom-directed physical examinations may be conducted at any time during the study, as deemed necessary by the investigator. Symptom-directed physical examinations may be conducted at any time during the study, as deemed necessary by the investigator.

[c] Temperature measurement is required only at screening and baseline.

[d] On days with concurrent ECG, vital sign, and/or PK sampling, these measurements should occur at approximately the same time. ECG recording and vital sign measurements should occur prior to the blood draw. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

[e] Times are referenced to end of dosing. ECGs will be obtained on Day [redacted] (predose [any time prior to dosing on the day of dosing, but within 90 minutes prior to the predose blood draw] and 6 h after dose and at any time on other specified visits (but prior to any blood draws at same visit).

f A posterior-anterior chest x-ray will be performed at screening unless one has been performed within the past 6 months and the x-ray and reports are available. Note: Results of a chest CT scan or other imaging study similar to a CXR may be substituted in place of the CXR as described above, in consultation with the Lilly's Clinical Pharmacologist.

g The follow-up TST reading should occur CCI days after screening.

h The following measures, NRS, POEM, and DLQI, should be completed prior to any clinical assessments being performed on days when study visits occur.

i Beta-D-glucan is required at screening (to be performed centrally), and if an investigator believes it is warranted, at subsequent visits (may be performed centrally or locally), a beta-D-glucan test may be included in the work up panel at any time during the study. If the beta-D-glucan test is positive, pneumocystis pneumonia (PCP) needs to be ruled out. If PCP is ruled out and the investigator deems the patient fit to continue, the patient may continue in the study. If a patient has a confirmed diagnosis of PCP during the study, the patient must discontinue the study.

j Includes IgA, IgM, IgD, IgE and IgG: to be done centrally. However, if results from central testing are delayed, then assessments can be done locally.

k A serum pregnancy test will be conducted at screening only. Urine pregnancy test will be used at all other time points. For women who are considered to be not of childbearing potential, FSH should be drawn to confirm status as defined in Inclusion Criterion [1b] and to be considered exempt for further pregnancy tests during the study.

l CCI

CCI

CCI

CCI

CCI

CCI

CCI

r Lesional and nonlesional skin images will be obtained. CCI

s At Day CCI lesional and nonlesional skin biopsies will be obtained. At Day CCI day, lesional and nonlesional skin biopsies will be obtained. Skin biopsies at all visits are optional.

t Failure to collect at the planned time points will not result in a protocol deviation.

1.3.3.2. Part C: CCI Dosing Schedule

Procedures/ Assessments	Screening	Treatment Period														Follow-up				ED
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	
Study Day(s)	CCI																			
Review/confirm I/E criteria	X	X																		
Informed Consent	X																			
Complete medical history	X																			
Review preexisting conditions/AEs	X	X[a]	X	X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X	X	X	X	X
Concomitant medications	X	X[a]	X	X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X	X	X	X	X
Previous and current AtD treatments	X																			
Substance use (alcohol, tobacco use)	X																			
Physical examination[b]	X																		X	X
Weight	X																		X	X
Height	X																			
Vital signs (heart rate, blood pressure, and temperature)[c,d]	X	X[a]	X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X	X	X	X	X
ECGs[d,e]	X	X					X					X							X	X

Procedures/ Assessments	**Screening**	**Treatment Period**														**Follow-up**				**ED**
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	
Study Day(s)	CCI																			
Chest x-ray[f] (posterior-anterior view)	X																			
IP administration	CCI																			
QuantiFERON®-TB Gold test or TST[g]	X																			
vIGA-AD	X	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
EASI	X	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
SCORAD	X	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
POEM[h]	X	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
DLQI[h]	X	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Itch numeric rating scale (NRS)[h]	X	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Beta-D-glucan[i]	X																			
Serologies (hepatitis B, hepatitis C, HIV) and syphilis testing	X																			
Serum immunoglobulins[j]	X						X				X				X				X	X
Urinary drug screen	X																			
FSH[k]	X																			

Procedures/ Assessments	Screening	Treatment Period													Follow-up				ED
Visit Number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	
Study Day(s)	CCI																			
Pregnancy test[k]	X	X		X	X	X	X	X	X	X	X	X	X	X	X				X	X
Clinical chemistry	X	X		X	X		X		X		X		X		X		X	X	X	X
Hematology	X	X		X			X				X		X		X		X	X	X	X
Urinalysis	X	X		X	X		X				X				X		X	X	X	X
Pharmacogenetics	CCI																			
Immunogenicity[l]																				
Blood samples for flow cytometry (safety)																				
CCI																				
CCI																				
CCI																				
Skin biopsies: nonlesional and lesional[s]		X													X					
CCI																				

Procedures/ Assessments	Screening	Treatment Period														Follow-up				ED
Visit Number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	
Study Day(s)	CCI																			
T-regulator proliferation panel 2[t]																				

Abbreviations: AE = adverse event; AtD= atopic dermatitis; CT = computed tomography; CXR = chest x-ray; CCI ; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; ED = early discontinuation; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; I/E = inclusion/exclusion; Ig = immunoglobulin; IP = investigational product; IV = intravenous; NRS = numeric rating scale; PCP = pneumocystis pneumonia; PK = pharmacokinetic; POEM = Patient-Oriented Eczema Measure; SCORAD = SCORing Atopic Dermatitis; TB = tuberculosis; TST = tuberculin skin test; V = visit; vIGA-AD = Validated Investigator's Global Assessment for Atopic Dermatitis.

Note: Missed CCI sample collection will not be considered a protocol deviation.

[a] At the discretion of the clinical site, the baseline measurement for this assessment can be collected at any time prior to dosing on the day of dosing.

[b] Full physical examination at screening, Day CCI and ED. Symptom-directed physical examinations may be conducted at any time during the study, as deemed necessary by the investigator. Symptom-directed physical examinations may be conducted at any time during the study, as deemed necessary by the investigator.

[c] Temperature measurement is required only at screening and baseline.

[d] On days with concurrent ECG, vital sign, and/or PK sampling, these measurements should occur at approximately the same time. ECG recording and vital sign measurements should occur prior to the blood draw. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

[e] Times are referenced to end of dosing. ECGs will be obtained on Day CCI (predose [any time prior to dosing on the day of dosing, but within 90 minutes prior to the predose blood draw] and 6 h after dose and at any time on other specified visits (but prior to any blood draws at same visit).

[f] A posterior-anterior chest x-ray will be performed at screening unless one has been performed within the past 6 months and the x-ray and reports are available. Note: Results of a chest CT scan or other imaging study similar to a CXR may be substituted in place of the CXR as described above, in consultation with the Lilly's Clinical Pharmacologist.

[g] The follow-up TST reading should occur CCI days after screening.

[h] The following measures, NRS, POEM, and DLQI, should be completed prior to any clinical assessments being performed on days when study visits occur.

[i] Beta-D-glucan is required at screening (to be performed centrally), and if an investigator believes it is warranted, at subsequent visits (may be performed centrally or locally), a beta-D-glucan test may be included in the work up panel at any time during the study. If the beta-D-glucan test is positive, pneumocystis pneumonia (PCP) needs to be ruled out. If PCP is ruled out and the investigator deems the patient fit to continue, the patient may continue in the study. If a patient has a confirmed diagnosis of PCP during the study, the patient must discontinue the study.

[j] Includes IgA, IgM, IgD, IgE, and IgG: to be done centrally. However, if results from central testing are delayed, then assessments can be done locally.

[k] A serum pregnancy test will be conducted at screening only. Urine pregnancy test will be used at all other time points. For women who are considered to be not of childbearing potential, FSH should be drawn to confirm status as defined in Inclusion Criterion [1b] and to be considered exempt for further pregnancy tests during the study.

[CCI] [redacted]



s At Day CCI lesional and nonlesional skin biopsies will be obtained. At Day CCI day, lesional and nonlesional skin biopsies will be obtained. Skin biopsies at all visits are optional.

t Failure to collect at the planned time points will not result in a protocol deviation.

2. Introduction

LY3844583 is composed of the Fab of a fully human antihuman GITR antibody fused via a flexible linker to the N-terminus of an albumin-binding VHH (variable region of the HC of a HC only antibody). The Fab portion of LY3844583 binds with high affinity to human and cynomolgus monkey GITR, which is expressed on various immune cells including T cells. Binding of LY3844583 to GITR potently antagonizes human and cynomolgus monkey GITRL. The Fab portion of LY3844583 is linked at the C-terminus of the HC via a flexible linker to the N-terminus of an albumin-binding VHH to extend half-life in vivo through high-affinity binding to human serum albumin.

LY3844583 is being investigated for the treatment of various autoimmune disorders involving dysregulation of T-cell activity including, but not limited to AtD.

2.1. Study Rationale

Study KKAA is the first-in-human dose study that will investigate the safety, tolerability, and PK of single- and multiple-ascending doses of LY3844583 in healthy participants and patients with AtD. An exploratory evaluation of CCI will be conducted following single and multiple doses of LY3844583 in healthy participants and patients with AtD. Exploratory assessments of CCI are also included. The data generated in this study will guide the design of subsequent clinical trials and will facilitate the inclusion of diverse ethnic groups in future clinical trials.

2.2. Background

GITR, also known as TNFRSF18, is a member of the TNFRSF and expressed on various immune cells including Tregs and activated T cells. GITR is a single-pass type I transmembrane protein and its extracellular domain consists of 3 cysteine-rich domains, which are typical of the TNFRSF. GITR is multimerized and activated upon interaction with its trimerized ligand GITRL (TNFSF18) resulting in induction of nuclear factor kappa B activation through TRAF2/TRAF5. The consequences of GITRL-induced GITR signaling include costimulation of T cell proliferation and cytokine release as well as abrogation of Treg suppressive effects.

Investigations have shown that GITR biology is associated with autoimmune disease and inflammatory responses. GITR knockout mice have reduced disease severity in mouse models. GITR activation, through either GITRL or GITR agonist antibody stimulation, causes disease worsening in mouse models of colitis, contact hypersensitivity, collagen inducted arthritis, experimental autoimmune encephalomyelitis, and type 1 diabetes. GITRL or GITR agonist antibody stimulation is associated with increased inflammation, T-cell differentiation, and cytokine release in those mouse models of disease. Given these observations, a GITR antagonist, without detectable agonist activity, may be a useful tool to treat autoimmune and inflammatory disease.

It has also been shown that GITR can be agonized through antibody binding and that this GITR activation may be further enhanced by agonist antibody binding to FcγRs; this enhancement is thought to be mediated by increased avidity or receptor multimerization. Therefore, a GITR antagonist is likely to exhibit agonist activity if it is bound on a surface, perhaps through binding

FcγRs on a cell surface, resulting in multimerization of GITR and subsequent activation. Thus, a monovalent anti-GITR antibody fragment that efficiently blocks GITR binding to its ligand and prevents receptor activation, without the ability to substantially engage FcγRs, is desired. The most straightforward way to ensure there is no possibility of FcγR engagement is to generate antibody fragments that entirely are devoid of the Fc domain.

LY3844583 is a recombinant fusion protein composed of the Fab of a fully human antihuman GITR antibody fused via a flexible linker to the N-terminus of an albumin-binding VHH (variable region of the HC of a HC only antibody). The Fab is composed of a human immunoglobulin G1 HC paired with a human kappa light chain. The Fab binds with high affinity to human and cynomolgus monkey GITR and potently antagonizes human and cynomolgus monkey GITRL. The Fab is linked at the C-terminus of the HC via a flexible linker to the N-terminus of an albumin-binding VHH, which serves to provide half-life extension via high affinity binding to human serum albumin.

The key characteristics of LY3844583 are listed below:

- binds human GITR with desirable association and dissociation rates (CCI [redacted]) for optimal antagonistic activity.
- contains an albumin-binding VHH that binds human serum albumin with a CCI [redacted] Is able to inhibit both GITRL costimulation of T cells and restore Treg suppressive activity inhibited by GITRL
- lacks detectable agonism of human GITR to achieve an immunosuppressive response
- causes no significant induction of cytokine release, and
- has sufficient PK and/or PD profiles and demonstrable in vivo efficacy in relevant T-cell-dependent inflammatory disease models using surrogate antibody as a monotherapy for the treatment and/or prevention of autoimmune disorders, allergic disease, asthma, or other inflammatory disorders.

Preclinical data

In vitro T-cell costimulation studies with activated primary human CD3+ T cells show LY3844583 is able to fully inhibit the co-stimulatory proliferation effect of GITRL and fully restore T regulatory suppression of T effector cell proliferation. In addition, the ability of a surrogate to LY3844583 to inhibit both T effector cells and restore Treg suppressive activity in vivo was monitorable in rodent models of immune and inflammatory disease involving T-cell dysregulation, including models of colitis and dermatitis.

Nonclinical toxicology data

In support of Phase 1 clinical development, the following nonclinical toxicity studies of LY3844583 were conducted and key findings were identified:

- A good laboratory practice-compliant, 3-month repeat-dose toxicity study in cynomolgus monkeys, in which definitive treatment-related effects were limited to nonadverse increases in serum globulins at the highest dose of CCI mg/kg CCI [redacted] by IV injection. As such, CCI mg/kg IV was the NOAEL. The NOAEL and its associated exposure provide CCI [redacted] dose and predicted exposure multiples to the maximum intended single dose of CCI mg IV in the SAD.

- A good laboratory practice-compliant, ex vivo cross-reactivity study with human and cynomolgus monkey tissues, in which most of the observed LY3844583 binding in each species was to mononuclear cells and consistent with the reported expression of GITR.
- An in vitro NK cell activity assay using human samples, which demonstrated no effects produced by LY3844583.
- In vitro cytokine release assays using human samples, which did not indicate a risk for CRS/cytokine storm in humans administered LY3844583.

Nonclinical pharmacokinetics and toxicokinetics data

The PK parameters of LY3844583 were determined in mice, rats, and monkeys. Overall, the PK parameters of LY3844583 indicate following points:

- SC bioavailability was CCI CCI and CCI in mice, rats, and monkeys respectively, when calculated comparing single CCI mg/kg SC and CCI mg/kg IV area under the plasma concentration-time curve from 0 to infinity ($AUC_{0-\infty}$) exposures and measured by antigen capture enzyme-linked immunosorbent assay with VHH detection.
- Nonlinear PK was observed in monkeys following low CCI to CCI mg/kg IV single doses of LY3844583, with mean terminal half-life increasing from CCI to CCI hours as the IV dose increased from CCI to CCI mg/kg.
- Following CCI CCI or CCI mg/kg SC doses, or CCI CCI mg/kg IV doses in monkeys, systemic exposure to LY3844583 increased in an approximately dose proportional manner with dose.
- After repeated SC dosing, accumulation was observed with accumulation ratios ranging between CCI and CCI in individual monkeys. After repeated IV bolus dosing, slight accumulation was observed with accumulation ratios ranging between CCI to CCI in individual monkeys.
- In vitro, the binding affinity of LY3844583 to serum albumin of different species was determined. The K_D of LY3844583 at 37°C was determined to be CCI nM for human serum albumin and CCI nM, CCI nM, and CCI nM for cynomolgus monkey, rat, and mouse serum albumin respectively, indicating high plasma protein binding across all 3 species.

Additional information regarding the in vitro and in vivo mechanism of action, toxicological, and PK or TK assessments of LY3844583 is available in the IB.

2.3. Benefit/Risk Assessment

The toxicology data for LY3844583 demonstrate an acceptable nonclinical safety profile and margin of safety to support the transition from preclinical status to a clinical single- and multiple-dose study in healthy participants and patients with AtD. While nonclinical safety studies have not identified specific risks, potential risks related to infusion reactions are considered to be monitorable and manageable in this study. There is no anticipated therapeutic benefit for the healthy participants in this trial. However, patients with AtD may derive therapeutic benefit from the trial.

In vitro T-cell costimulation studies with activated primary human CD3+ T cells show LY3844583 is able to fully inhibit the co-stimulatory proliferation effect of GITRL and fully

restore T regulatory suppression of T effector cell proliferation. Moreover, LY3844583 does not contain a Fc region, thus binding to binding FcγRs on a cell surface (which may cause GITR activation) is unlikely. In addition, the ability of LY3844583 to inhibit both GITRL costimulation of T cells and restore Treg suppressive activity inhibited by GITRL in vivo was monitorable in rodent models of immune and inflammatory disease involving T-cell dysregulation. Furthermore, LY3844583 lacks detectable agonism of human GITR. Based upon these data, there is no anticipated pharmacological effect of LY3844583 target engagement in a healthy participant population. As LY3844583 is an antagonist, it is expected to produce pharmacological effect in an AtD patient population. GITR knockout mice have reduced disease severity in mouse models and GITR antagonism in T-cell-mediated immune and inflammatory disease have shown improvement of disease. As such, flow cytometry will be used to monitor circulating levels of T cells and other immune cell subtypes (NK and B cells) in healthy participants and patients with AtD. Along with PK, the kinetics of CCI will also be assessed on peripherally circulating T cells in healthy participants for an understanding of the CCI relationship. Immunoglobulins will also be monitored in heathy participants over time. Refer to Section 8.8 for further details.

As with other immunomodulatory therapies, LY3844583 may increase the risk of developing infections or may increase the risk of an infection becoming more serious and/or may change the effectiveness of vaccines administered. Opportunistic infections and reactivation of latent infections may include hepatitis B. Participants will therefore be screened for hepatitis B, hepatitis C, HIV, and TB. In addition, all participants should be monitored for symptoms and signs of infection after administration of LY3844583.

LY3844583 has not been administered to humans previously. Therefore, this study has been designed in accordance with the Guideline on Strategies to Identify and Mitigate Risks for First-in-human Clinical Trials with Investigational Medicinal Products (EMA 2017, PSEHB/ELD 2019). More information about LY3844583 is provided in the IB.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of LY3844583 after single and multiple dose administrations in healthy participants and after repeat-dose administration in the participants with AtD.	• Incidence of AEs, TEAEs, and SAEs
Secondary	
• To characterize the PK of LY3844583 following single- and multiple-dose administrations in healthy participants and after repeat dosing in participants with AtD.	• C_{max} and AUC
Exploratory	

CCI

Objectives	Endpoints
CCI	

Abbreviations: AE = adverse event; AtD = atopic dermatitis; AUC = area under the concentration versus time curve; C_{max} = maximum observed drug concentration; CCI ; CCI ; PK = pharmacokinetics; SAE = serious adverse event; CCI ; TEAE = treatment-emergent adverse event; CCI ; CCI ; CCI

Estimands

TEAEs and SAEs will be listed and, if the frequency of events allows, descriptive statistics will summarize the safety data per race and ethnicity. Symptoms, their incidence, severity, and association with IP, as perceived by the investigator, will be reported separately for each treatment. All TEAEs will be summarized across each part of the study by system organ class and by decreasing frequency according to the Medical Dictionary for Regulatory Activities.

4. Study Design

4.1. Overall Design

Study KKAA is a first-in-human trial designed to evaluate safety, tolerability, PK and target engagement of LY3844583 in healthy participants and participants with AtD, with additional assessments of clinical PD and efficacy in participants with AtD. The inclusion of healthy Japanese and Chinese participants in this study will facilitate the inclusion of Japanese and Chinese participants in subsequent clinical trials. The study will be conducted in 3 parts as follows:

- Part A (SAD) will assess the safety, tolerability, PK, and CCI of single SC and IV doses of LY3844583 in healthy participants.
- Part B (MAD) will assess the safety, tolerability, PK, and CCI of multiple IV and/or SC doses of LY3844583 in healthy participants.
- Part C (repeat dose) will assess the safety, tolerability, PK, CCI and exploratory data of multiple IV or SC doses of LY3844583 in participants with AtD.

Table KKAA.1 provides a detailed description of participants enrolled in each cohort and planned doses for Parts A, B, and C. Section 1.2 illustrates the study schema and demonstrates the relationship among Parts A, B, and C. Part A will begin first and will inform and thereby trigger the initiation of Parts B and C.

The study will consist of 3 periods.

Screening period for SAD Part A, MAD Part B, and repeat-dose Part C

Screening may occur up to CCI days prior to Day CC of the study. After obtaining informed consent, participants will be screened for eligibility as detailed in Section 5. Screening procedures will be performed as outlined in Section 1.3.

Participants who are not enrolled within CCI days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility. The assessments will be repeated at the discretion of the investigator.

Treatment period

SAD Part A

Part A will be a SAD study and will be comprised of 5 cohorts and 2 optional cohorts. Each cohort will consist of approximately CC healthy participants, who will be randomized to receive LY3844583:placebo in a CCI manner at each dose level, except Cohort 5, who will be randomized to receive LY3844583:placebo in a CCI manner. See Table KKAA.1 for further details. Optional Cohorts 6 and 7 may be enrolled depending on emerging data from earlier cohorts.

The planned doses are CCI mg SC (Cohort 1), CCI mg SC (Cohort 2), CCI mg SC (Cohort 3), CCI mg IV (Cohort 4), and CCI mg IV (Cohort 5). Study intervention will be administered as a single dose on Day CCI followed by a CCI-week follow-up period. Dose escalation will be based on the review of available data from the ongoing cohorts. The dose for optional Cohorts 6 and 7 will

be decided based on emerging data from earlier cohorts. Refer to Sections 6.5 and 6.5.1 for further details on dose escalation.

A sentinel dosing strategy will be utilized in Cohorts 1 and 2 to minimize the participant risk. The initial 2 participants in each of these cohorts will be randomized to receive LY3844583:placebo in a CCI manner on the same day. With sentinel dosing, only 1 participant will be dosed at a time, and the second participant will not be dosed until the first participant's administration is complete. The maximal concentration of LY3844583 following SC administration is uncertain and is projected to occur approximately CCI [redacted], which is similar to reports for antibody therapies (Ryman and Meibohm 2017). Thus, after at least [redacted] days of postsentinel dosing, the remaining participants in the cohort will be dosed based on the available safety and tolerability data.

The participants in the CCI mg IV and CCI mg IV cohorts will be dosed in sequence, each following, at a minimum, at least approximately 1 hour after the completion of the administration for the prior participant. Refer to Section 6.5 for details on data review prior to dosing.

Participants will be monitored for safety, including ISRs, and samples will be collected as outlined in Section 1.3.1. Participants will be discharged from the CRU on Day [redacted] after all study assessments have been completed during the treatment period and in agreement with the investigator.

MAD Part B

Part B will be a MAD study in healthy participants and will comprised of 2 cohorts to assess any acute safety/tolerability events associated with a second and/or third exposure. See Table KKAA.1 for further details.

After the first dose on Day [redacted] participants will undergo clinical assessments, safety monitoring, and samples will be collected. Participants will be discharged from the CRU at the discretion of the investigator at time points as mentioned in SoA (Section 1.3.2). In Cohort 1, participants will receive up to [redacted] additional doses on Days [redacted] and [redacted] In Cohort 2, participants will receive up to [redacted] additional doses on Days [redacted] and [redacted] Participants will be required to visit the CRU on an outpatient basis for clinical assessments and sample collection.

The planned doses are [redacted] mg IV [redacted] in Cohort 1 and ≤[redacted] mg IV or SC [redacted] in Cohort 2. The route and frequency will be confirmed based on the emerging data from SAD cohorts. A decision regarding the MAD Cohorts 1 and 2 doses will be taken following review of available data from Part A of the study. Refer to Sections 6.5 and 6.5.1.2 for further details on dose escalation.

Repeat-dose Part C

Part C will be a repeat-dose study in up to [redacted] patients with AtD with [redacted] LY3844583 and [redacted] placebo.

The planned dose is ≤[redacted] mg SC or IV. Study intervention will be administered on Day [redacted] followed by dose administration [redacted] or [redacted] for [redacted] weeks. The dose will be administered at the discretion of the investigator and in discussion with the sponsor.

Specific requirements for commencement of Part C are discussed in Section 6.5.1.3.

For all study parts

The timings and procedures are outlined in Section 1.3. If the investigator deems it necessary, participants may remain in the CRU for a longer duration. Any changes to the planned discharge day will be made in consultation with the sponsor.

Participants in all parts of the study should follow local guidance and CRU precautions to minimize risk for infection, including Coronavirus Disease 2019.

Follow-up period for SAD Part A, MAD Part B, and repeat-dose Part C

Participants will be required to return to the CRU for clinical assessments and blood samples on an outpatient basis (Section 1.3). The final follow-up visit will be approximately CCI weeks after single dose in Part A, CCI weeks after the last dose of study intervention in Part B, and CCI weeks after the last dose of study intervention in Part C.

Table KKAA.1. Summary of Participant Cohorts

Cohort #	Planned Dose/Administration Route	Number of Planned Non-Japanese/Non-Chinese Participants		Number of Planned Japanese Participants		Number of Planned Chinese Participants		Total Number of Planned Completers
		LY	PBO	LY	PBO	LY	PBO	
SAD Part A								
SAD Cohort 1[a]	Dose/Route CCI mg SC	CCI						
SAD Cohort 2[a]	Dose/Route CCI mg SC							
SAD Cohort 3	Dose/Route CCI mg SC							
SAD Cohort 4	Dose/Route CCI mg IV							
SAD Cohort 5	Dose/Route CCI mg IV							
SAD Cohort 6 (optional)	Dose/Route TBD							
SAD Cohort 7 (optional)	Dose/Route TBD							
MAD Part B								
Multiple-Dose Cohort 1	Dose/Route CCI mg IV							

Cohort #	Planned Dose/Administration Route	Number of Planned Non-Japanese/Non-Chinese Participants		Number of Planned Japanese Participants		Number of Planned Chinese Participants		Total Number of Planned Completers
		LY	PBO	LY	PBO	LY	PBO	
Multiple-Dose Cohort 2	Dose/Route ≤CCI mg IV or SC	CCI						
Repeat-dose Part C								
Atopic Dermatitis	Dose/Route ≤CCI mg SC or IV							

Abbreviations: IV = intravenous; LY = LY3844583; MAD = multiple-ascending dose, PBO = placebo; SAD = single-ascending dose; SC = subcutaneous; TBD = To be Decided.

[a] Sentinel dosing will be used in this cohort.

[b] The allocation ratio is CCI. The stated ratio is only observed if CCI patients are enrolled.

[c] Minimum number of completers.

4.2. Scientific Rationale for Study Design

The LY3844583 pharmacology and toxicology data support that the safety of LY3844583 can be appropriately evaluated in healthy participants and patients with AtD. Conducting the study in healthy participants (Parts A and B) mitigates the potential confounding effects of disease states and concomitant medications. Based on the anticipated mechanism of action, target expression profile, and supporting preclinical data, LY3844583 is expected to have a therapeutic effect in reducing signs and symptoms of autoimmune diseases, including AtD (Part C). Thus, an initial assessment of therapeutic effect will be assessed in AtD to inform future development of the compound for this indication.

All parts of the study will be conducted in CRUs to maximize appropriate safety oversight and to assess the safety, tolerability, PK, and target engagement of LY3844583. Participants and investigators are blinded to study treatments to minimize bias during the data collection.

Japanese and Chinese participants are included for ethnic comparisons of safety, tolerability, and PK and enables inclusion of these populations into the next stages of development.

This is a sequential design study based on preclinical PK data. LY3844583 is projected to have a half-life of approximately CCI to CCI days, thus a crossover design would require a long washout period. In addition, there is the potential for development of anti-LY3844583 antibodies, which could confound analyses for subsequent doses in a crossover design. This study design is commonly used for the assessment of safety and tolerability of mAb and mAb-like modalities.

Sentinel dosing will be used in SAD Cohorts 1 and 2 to minimize participant risk as this Phase 1 will be the first assessment of the safety, tolerability, PK, and CCI of LY3844583 in human

participants. SAD Cohort 2 will be studied using a staggered dosing approach described in Section 6.5.1. The rationale to escalate in a staggered dosing approach from Cohort 1 to Cohort 2 is based on

- the projected exposure multiple based on NOAEL ≥CCI for Cohort 2, and
- the availability of human safety/tolerability data from the Cohort 1 sentinel dosing at least CCI days post-administration and when at least CCI days has elapsed providing adequate decision-making information to proceed with administration of the remaining participants in Cohort 1 and the sentinel dosing of Cohort 2 concurrently.

Inclusion of SC and IV administration at the same dose level in SAD Cohorts 3 and 4 will provide a preliminary assessment of SC bioavailability. Additionally, SAD Cohorts 3 and 4 will be studied using a concurrent dosing approach described in Section 6.5.1. The rationale for a concurrent dosing approach is based on:

- the projected exposure multiples based on NOAEL ≥CCI for SAD Cohorts 3 and 4, and
- the availability of human safety/tolerability data from at least CCI participants from SAD Cohorts 1 and 2 when at least CCI days has elapsed after the administration nonsentinel dosing participants in Cohort 2 to provide adequate decision-making information to proceed with administration in Cohort 3 and 4 concurrently.

Based on the predicted human PK, ≥CCI% of LY3844583 is expected to be eliminated from the systemic circulation in the planned CCI-week follow-up period following the last administration of LY3844583 in the SAD (Part A) and MAD (Part B) cohorts. Thus, a CCI-week follow-up period is expected to be sufficient in duration to characterize safety, tolerability, PK, and CCI of study intervention for SAD (Part A) and MAD (Part B) cohorts.

In Part C, a CCI-week treatment period is planned as this is a standard duration for AtD trials and will therefore enable a comparison to the effects of other therapies. Considering the potential greater LY3844583 accumulation over the longer treatment period in Part C (relative to Parts A and B), a CCI-week follow-up period is planned.

However, if after the applicable follow-up period, from the last administration of LY3844583, sustained CCI on T cells is observed without evidence of a decline, then the sponsor will continue an additional extended follow-up period to monitor CCI approximately once every CCI months up to approximately CCI months after the last dose of LY3844583. In addition, samples for other parameters including circulating immunoglobulin levels, WBC subpopulations, immunogenicity, and PK may also be collected during the extended follow-up at the discretion of the sponsor. Symptom driven safety assessments and safety data collections may also be collected during the extended follow-up period at the discretion of the Principal Investigator and in discussion with the sponsor.

4.3. Justification for Dose

A dose range of CCI mg SC to CCI mg SC and from CCI mg IV to CCI mg IV LY3844583 was selected to evaluate in the SAD part of the study based on current nonclinical pharmacology and toxicology data.

Human PK prediction procedure

Because nonlinear PK were observed in a cynomolgus monkey study and the approach to scale nonlinear PK from monkey to human was not fully established, 2 following methods were adopted to project LY3844583 human PK:

- Allometric scaling method with fixed exponents of CCI for linear clearance, V_{max}, and intercompartmental clearance, [redacted] for volume, and CCI for the first order SC absorption rate constant. Estimate for Michaelis-Menten constant in the nonlinear elimination term was not scaled (Dong et al. 2011).
- Allometric scaling method with fixed exponents of CCI for linear clearance and intercompartmental clearance, [redacted] for volume, and CCI for the first order SC absorption rate constant. Both estimates for Michaelis-Menten constant and V_{max} were not scaled.

Based on reported bioavailability (%F), approximately CCI for mAbs by Ryman and Meibohm (2017), Eli Lilly and Company (Lilly) in-house data for monkey-to-human PK translation, and considering that LY3844583 is smaller than mAb, human SC bioavailability of LY3844583 was assumed to be in the range of CCI% to CCI% following a normal distribution with mean of CCI% (bioavailability of LY3844583 in monkeys) and CCI% coefficient of variance. With CCI% bioavailability and for a typical 70 kg subject, the terminal half-life at high doses, for example, CCI mg to CCI mg IV, is projected approximately CCI to CCI days with consideration of scaling V_{max} or CCI to CCI days without scaling V_{max} when PK was as approximately linear even at lower doses.

Human dose-prediction procedure

Given that in vivo pharmacology data were not available for LY3844583, binding affinity of LY3844583 to human GITR-expressing Jurkat cells under equilibrium conditions was adopted to support human dose-prediction. The percent of membrane GITR occupied on plasma-resident immune cells and tissue-resident immune cells (CCI were estimated using a maximum effect model, in which the half-maximal effective concentration was assumed to be equal to the equilibrium LY3844583 binding affinity to human GITR-expressing Jurkat cells (K_D = CCI pM or CCI ng/mL assuming a molecular weight of CCI kDa). Considering the antagonist mechanism of LY3844583, a high level of target engagement is assumed to be required for efficacy (for example, >CCI%) to account for the uncertainty with use of CCI as a surrogate for pharmacological activity.

LY3844583 is a recombinant fusion protein composed of GITR-binding Fab domain, fused via a flexible linker to an albumin-binding VHH domain. The VHH domain binds a single albumin molecule with pM to nM affinity (albumin molecular weight of approximately CCI kDa). Given the abundance of albumin in vivo, the majority LY3844583 in blood and tissue is expected to exist as an albumin-bound LY3844583 complex, thus with an apparent size close to that of a monoclonal antibody. Thus, antibody distribution coefficients in noncentral nervous system tissues were assumed to be applicable to albumin-bound LY3844583 with a tissue-plasma partition coefficient uniformly distributed in the range of CCI% to CCI% (Shah and Betts 2013).

Using the assumptions and estimates described above, PK and PK/PD simulations were conducted to provide exposure estimates and predicted CCI in plasma and in tissue at various doses in humans across a range of doses. Considering majority study participants will be non-Japanese/non-Chinese and reported body weight distribution for Caucasian (Male: 80.2 ± 11.0 kg, Female: 62.7 ± 10.4 kg), Chinese (Male: 65.8 ± 8.61 kg, Female: 57.0 ± 7.24 kg), and Japanese (Male: 65.34 ± 9.83 kg, Female: 52.99 ± 7.88 kg) (Okamoto et al. 2017; Gallagher

et al. 2000; Zou et al. 2017), simulation was carried out assuming a representative body weight of 70 kg. If 60 kg body weight is assumed, the exposure multiple at the CCI mg IV SAD is predicted to be approximately CCI .

SAD starting dose

The proposed SAD starting dose is CCI mg SC, which is supported by the following information (Section 2.3):

- No adverse effects were identified in the 3-month repeat-dose toxicology study in monkeys. A NOAEL of CCI mg/kg IV was established.
- The predicted exposure in humans given a dose of CCI mg SC is CCI below exposure at the NOAEL in monkeys (Table KKAA.2).
- LY3844583 was demonstrated not to stimulate cytokine release in vitro assays using human samples and therefore has a low risk of producing CRS in humans.
- LY3844583 has an antagonist action, which can inhibit both GITRL costimulation of T cells and restore Treg suppressive activity inhibited by GITRL but does not have detectable agonism of human GITR to achieve an immunosuppressive response (Section 2.3). This suggests binding of LY3844583 to GITR may not alter activation on effector T cells or Tregs under a normative state.
- Given its overall preclinical toxicity profile and mechanism of action, LY3844583 is considered as a low-risk molecule and supports a safe clinical starting dose above a minimum anticipated biological effect level (Leach et al. 2021).

Based on PK/PD modeling, this dose is predicted to achieve

- Median blood CCI of 98.9% (96.4% to approximately 99.5% - projected 5 to 95 percentile) at Week CCI using methods with V_{max} scaling or 99.5% (99% to approximately 99.8%) at Week CCI without V_{max} scaling.
- Median tissue CCI of 89.7% (66.9% to approximately 95.9%) at Week CCI with V_{max} scaling or 95.2% (87.9% to approximately 98.1%) at Week CCI without V_{max} scaling.

SAD maximum dose

To achieve optimal efficacy, LY3844583 may need to engage tissue-resident immune cells. Thus, to ensure adequate concentrations will be achieved to saturate the receptor in the target tissue, the maximum dose proposed in this study is CCI mg IV. The monkey NOAEL provides predicted exposure multiples of approximately CCI to CCI mg IV (Table KKAA.2). Dose escalation and modification details can be found in Section 6.5.

Based on PK/PD modeling, this dose is projected to achieve:

1. sustained median plasma CCI >95% for at least CCI weeks, and
2. sustained median tissue CCI >95% for at least CCI weeks.

Table KKAA.2. NOAEL-based Dose and Model-predicted Exposure Multiples for Proposed Single and Repeated Administrations of LY3844583 to Human Participants

	Dose (mg/kg) and Frequency	Dose Multiple (mg/m^2)[a]	AUC (µg•hr/mL)	$C_{av,ss}$ (µg/mL)	Exposure Multiple[b]
Human SAD starting dose: CCI mg SC SAD highest dose: CCI mg IV MAD highest dose: CCI mg SC MAD highest dose: CCI mg IV	CCI				
Monkey NOAEL[h]: CCI mg/kg IV					

Abbreviations: AUC = area under the curve; $AUC_{0\text{-}168,ss}$ = area under the curve from time 0 to 168 hours at steady state; $AUC_{0\text{-}\infty}$ = area under the curve from time 0 to infinity; C_{av} = average concentration; $C_{av,ss}$ = average concentration at steady state; IV = intravenous; MAD = multiple-ascending dose; NOAEL = no-observed-adverse-effect level; CCI ; SAD = single-ascending dose; SC = subcutaneous; V_{max} = maximum velocity of the elimination.

[a] Dose multiple is the dose in animals/planned dose in humans based on body surface area (mg/m2). The mg/kg dose is multiplied by 37 for human and by 12 for monkey to convert to mg/m2 dose.

[b] Exposure multiple is the AUC or C_{av} at steady state in monkeys/predicted AUC or C_{av} in humans. For single-dose administration in the SAD portion of the first-in-human study, monkey $AUC_{0\text{-}168,ss}$/predicted human $AUC_{0\text{-}\infty}$ is used to calculate a conservative estimate of exposure multiple. For the MAD portion of the first-in-human study, $C_{av,ss}$ values are used.

[c] Flat dose converted to mg/kg dose using a 70-kg body weight.

[d] Predicted human $AUC_{0\text{-}\infty}$ using allometric scaling of single dose cynomolgus monkey data.

[e] Most conservative results from projection without scaling V_{max} and projection with scaling V_{max}.

[f] $C_{av,ss}$ is calculated using estimated $AUC_{0\text{-}\infty}$ (CCI µg•hr/mL) following a single CCI mg SC dose/168 hours given planned CCI dosing.

[g] $C_{av,ss}$ is calculated as $AUC_{0\text{-}\infty}$ (CCI µg•hr/mL) following a single CCI mg IV dose/168 hours given planned CCI dosing.

[h] NOAEL determined from 3-month repeat-dose toxicology data in cynomolgus monkeys.

[i] Mean $AUC_{0\text{-}168hr}$ measured at steady-state in male and female monkeys.

[j] $C_{av,ss}$ is calculated as $AUC_{0\text{-}168hr}$/168 hours.

All proposed SAD dose levels

For the subsequent cohorts in the SAD, planned doses were selected based on the predicted 5th percentile of tissue CCI >95% for at least [redacted] weeks to maintain the exposures and ensure 95% of

subjects achieving the desired tissue CCI Table KKAA.3 and Table KKAA.4 show the predicted AUC, maximum and Day CCI and Day CCI blood and tissue CCI, and exposure multiples to the NOAEL doses for each planned dose in the SAD study with/without scaling of nonlinear elimination V_{max}.

Table KKAA.3. Predicted PK/PD and Exposure Multiples to NOAEL Doses for Planned SAD Doses with Scaling of Vmax

Dose (mg)	AUC[a]$_{0-\infty}$ (µg*hr/mL)	Blood CCI[b] (%) at max	Blood CCI (%) Day CCI	Blood CCI[c] (%) Day CCI	Tissue CCI (%) at max	Tissue CCI[c] (%) at Day CCI	Tissue CCI (%) at Day CCI	Exposure Multiple to NOAEL AUC$_{0-168}$ (1,910,000 µg*hr/mL)
CCI mg SC	CCI							
CCI mg SC								
CCI mg SC								
CCI mg IV								
CCI mg IV								

Abbreviations: AUC_{0-168} = area under the curve from time 0 to 168 hours; $AUC_{0-\infty}$ = area under the concentration versus time curve from 0 to infinity; IV = intravenous; max = maximum; NOAEL = no-observed-adverse-effect level; PD = pharmacodynamic; PK = pharmacokinetic; CCI; SAD = single-ascending dose; SC = subcutaneous; V_{max} = maximum velocity of the elimination.

[a] Projected geometric mean.

[b] Projected arithmetic mean.

[c] Projected median and 5 to 95 percentiles.

Table KKAA.4. Predicted PK/PD and Exposure Multiples to NOAEL Doses for Planned SAD Doses without Scaling of Vmax

Dose (mg)	$AUC_{0-\infty}$[a] (µg*hr/mL)	Blood CCI (%) at max	Blood CCI (%) at Day [redacted]	Blood CCI (%) at Day CCI	Tissue CCI (%) at max	Tissue CCI (%) at Day [redacted]	Tissue CCI[c] (%) at Day CCI	Exposure Multiple to NOAEL AUC_{0-168} (1,910,000 µg*hr/mL)
CCI mg SC	CCI							
CCI mg SC								
CCI mg SC								
CCI mg IV								
CCI mg IV								

Abbreviations: AUC0-168 = area under the curve from time 0 to 168 hours; AUC0-∞ = area under the concentration versus time curve from 0 to infinity; IV = intravenous; max = maximum; NOAEL = no-observed-adverse-effect level; PD = pharmacodynamic; PK = pharmacokinetic CCI; SAD = single-ascending dose; SC = subcutaneous; V_{max} = maximum velocity of the elimination.

[a] Projected geometric mean.

[b] Projected arithmetic mean.

[c] Projected median and 5 to 95 percentiles.

MAD dosing

The dose for the MAD Part B Cohort 1 will be CCI mg IV CCI for a total of [redacted] doses on Days CCI

The dose for the MAD Part B Cohort 2 of the study is planned as ≤CCI mg CCI IV or SC for a total of [redacted] doses on Days CCI. The route of administration for this cohort will be confirmed based on emerging SAD and MAD Cohort 1 data.

Repeat dosing

For Part C, at least 1 dose cohort is planned for patients with AtD. Initial dose will be ≤CCI mg given CCI for a total of [redacted] doses on Days CCI or CCI for a total of CCI doses on Days CCI. The route could be IV or SC based on emerging data from SAD Part A and MAD Part B cohorts. Based on estimated human exposure, the NOAEL from monkey toxicology study provides margin of safety CCI to a repeated dose of CCI mg CCI or CCI to a repeated dose of CCI mg CCI (Table KKAA.2).

Dose escalation and modification details for MAD Part B and Part C can be found in Section 6.5.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA (Section 1.3) for the last participant in the trial globally.

A participant is considered to have completed the study if the participant has completed all periods of the study including the last visit or the last scheduled procedure shown in the SoA (Section 1.3).

5. Study Population

Eligibility of participants for enrollment in the study will be based on the results of screening assessments. The nature of any conditions presented at the time of the physical examination and any preexisting conditions will be documented. The inclusion and exclusion criteria used to determine eligibility should be applied at screening only unless otherwise specified and not continuously throughout the trial. Screening may occur up to [redacted] days prior to enrollment. Participants who are not enrolled within [redacted] days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible for inclusion in the study only if they meet all of the following criteria at screening and/or enrollment:

[1] are overtly healthy, for Parts A and B, as determined by medical history and physical examination.

- To qualify as Japanese for the purpose of this study, the participant must be first-generation Japanese, defined as the participant's biological parents and all of the participant's biological grandparents must be of exclusive Japanese descent, and must have been born in Japan.
- To qualify as Chinese for the purpose of this study, the participant must be at a minimum, third-generation Chinese, defined as all 4 of the participants' biological grandparents must be of exclusive Chinese descent and born in China.

[1a] Male participants:

- Please refer to Section 10.4 for definitions and additional guidance related to contraception.

[1b] Female participants:

- Women not of childbearing potential may participate in this study. Please refer to Section 10.4 for definitions and additional guidance related to contraception.

[2] are between 18 and 65 years of age, inclusive, at the time of screening.

[3] have a body mass index of 18.0 to 32.0 kg/m^2, inclusive, for Parts A and B, and 18.0 to 45.0 kg/m^2, inclusive, for Part C. For healthy Japanese participants, have a body mass index of 18.0 to 28.0 kg/m^2, inclusive, and a body weight of 50 kg to 85 kg, inclusive.

[4] have clinical laboratory test results within normal reference range for the population or investigative site or results with acceptable abnormalities that are judged to be not clinically significant by the investigator.

[5] have venous access sufficient to allow for blood sampling and administration of IP for IV administration as per the protocol.

[6] are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.

[7] are able and willing to give signed informed consent.

[8] have blood pressure, PR, and an ECG reading that is considered to be within normal limits as determined by the investigator.

5.1.1. Additional Inclusion Criteria for Part C (Patients with AtD)

[9] Female participants:

- Women not of childbearing potential and WOCBP may participate in Part C of this study. Please refer to Section 10.4 for definitions and additional guidance related to contraception.

[10] have a diagnosis of AtD at least 12 months prior to screening as defined by the American Academy of Dermatology (Eichenfield et al. 2014).

[11] have AtD, including all of the following:

[11a] EASI score ≥12 at screening (Visit 1) and at randomization (Visit 2)

[11b] vIGA-AD score of ≥3 at screening (Visit 1) and at randomization (Visit 2)

[11c] ≥7% of body surface area involvement at screening (Visit 1) and at randomization (Visit 2)

[12] have a history, documented by a physician and/or investigator, of inadequate response to existing topical medications within 6 months preceding screening, or a history of intolerance to topical therapy as defined by at least 1 of the following:

[12a] Inability to achieve good disease control defined as mild disease or better (for example, vIGA-AD ≤2) after use of at least a medium potency topical corticosteroid (TCS) for at least 4 weeks or for the maximum duration recommended by the product prescribing information (for example, 14 days for super-potent TCS), whichever is shorter. TCSs may be used with or without topical calcineurin inhibitors (TCNIs).

[12b] Documented history of clinically significant adverse reactions with the use of TCS such as skin atrophy, allergic reactions, or systemic effects that, in the opinion of the investigator, outweighs the benefits of retreatment.

[12c] Participants who failed systemic therapies intended to treat AtD, such as cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil,

within 6 months preceding screening, will also be considered as having inadequate response to topical therapy.

[13] agree to discontinue use of the following excluded medications for at least 2 weeks prior to randomization (Visit 2) and throughout the study:

[13a] Topical corticosteroids or topical immune modulators (for example, tacrolimus)

[13b] topical phosphodiesterase type 4 inhibitor

[13c] topical Janus kinase inhibitor

[14] have applied emollients daily for at least 14 days prior to randomization and agree to use emollient daily throughout the treatment period.

[15] who are receiving chronic treatments to improve sleep should be on a stable dose for at least 2 weeks prior to screening as determined by the investigator.

[16] who are not taking sedating antihistamines (see Exclusion Criterion 46c).

5.2. Exclusion Criteria

Participants will be excluded from study enrollment if they meet any of the following criteria at screening and/or enrollment:

[17] are investigative site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling.

[18] are Lilly employees or are employees of a third-party organization involved with the study.

[19] are currently enrolled in a clinical study involving an IP or any other type of medical research judged not to be scientifically or medically compatible with this study or have received any nonbiologic or biologic agent (such as monoclonal antibodies, including marketed drugs) within 30 days or 5 half-lives (whichever is longer) of randomization.

[20] have previously completed a clinical trial investigating any other molecule targeting interleukin-33 and/or the interleukin-33 receptor (ST2).

[21] have a current or recent acute, active infection (for example, for at least 30 days before screening and up to the randomization visit, participants must have no symptoms or signs of infection in the absence of any, anti-infective treatment).

[22] have received live vaccine(s) (including attenuated live vaccines) or Bacillus Calmette-Guérin within 28 days of screening or intend to receive them during the study (non-live or inactivated vaccinations are allowed).

[23] have had any of the following types of infection within 3 months prior to the screening visit or develops any of these infections before the randomization visit:

- Serious (requiring hospitalization or IV or equivalent oral antibiotic treatment, or both)
- Opportunistic (as defined in Winthrop et al. 2015)
  Note: Herpes zoster is considered active and ongoing until all vesicles are dry and crusted over.
- Chronic (duration of symptoms, signs, and/or treatment of 6 weeks or longer)
- Recurring (including, but not limited to, herpes simplex, herpes zoster, and recurring cellulitis.

[24] show evidence of active or latent TB, as documented through medical history and examination, chest x-rays (posterior to anterior, read by a radiologist, pulmonologist, or designee; a lateral chest x-ray may be performed if clinically or radiologically indicated), and TB testing: either a positive tuberculin skin test (TST; defined as a skin induration >5 mm at 48 to 72 hours, regardless of Bacillus Calmette-Guérin or other vaccination history) or a positive QuantiFERON®-TB Gold test. If the QuantiFERON-TB Gold test result is indeterminate, it may be repeated only once and, if the repeat test is indeterminate, the participant will be deemed ineligible. The choice to perform a TST or a QuantiFERON-TB Gold test will be made by the investigator according to local standard of care. Please note if a chest x-ray has been performed in the past 6 months, found to be normal and the report is available, a further chest x-ray is not required provided there is no known TB exposure since the x-ray was performed.

[25] had any surgical procedure (except for minor surgery requiring local or no anesthesia and without any complications or sequelae) within 12 weeks prior to screening or any planned surgical procedure scheduled to occur during the study.

[26] have a history or presence of multiple or severe allergies, or an anaphylactic reaction, to prescription or nonprescription drugs.

[27] have a history or presence of allergy to mAbs, or have clinically significant multiple or severe drug allergies, intolerance to TCSs, or a history of severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis).

[28] had any malignancy within the past 5 years. Exceptions: successfully treated basal cell skin carcinoma or squamous cell skin carcinoma, with no evidence of recurrence or metastatic disease within the 3 years prior to baseline.

[29] current smoker using >10 cigarettes or other tobacco products per day. Are unable/unwilling to stop smoking tobacco products while in the study unit.

[30] are regular users of known drugs of abuse and/or have positive findings on urinary drug tests at screening, OR an average weekly alcohol intake that exceeds 21 units per week (males) or 14 units per week (females), OR are unwilling to stop alcohol consumption during study visits/time in the research unit (1 unit of alcohol = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits).

[31] have donated blood of more than 500 mL within the previous 30 days of study screening.

[31a] for Chinese participants:

- have donated blood of more than 400 mL within the previous 30 days of study screening.

[32] have known hypogammaglobulinemia or a screening serum immunoglobulin G <565 mg/dL, immunoglobulin M <40 mg/dL, or immunoglobulin A <70 mg/dL.

[33] are immunocompromised.

[34] have presence of significant uncontrolled cerebro-cardiovascular (for example, myocardial infarction, unstable angina, hypertension, moderate to severe [New York Heart Association Class III/IV] heart failure, or cerebrovascular accident), respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neurologic or neuropsychiatric disorders or abnormal laboratory values at screening that, in the opinion of the sponsor or investigator, pose an unacceptable risk to the participant if participating in the study or of interfering with the interpretation of data.

[35] use or intend to use herbal, over-the-counter, or prescription medication within 14 days prior to dosing and during the study, other than estrogen/progesterone as a form of hormone replacement therapy and/or oral contraceptive. Certain medications (for example, vitamin supplements or prescription medications) may be permitted at the discretion of the investigator and in agreement with the sponsor. For Part C, see additional exclusion criteria.

[36] have 1 of the following viral infections:

[36a] a current infection with HBV (that is, positive for HBsAg and/or polymerase chain reaction (PCR) positive for HBV DNA; Section 8.2.8).

[36b] a current infection with HCV (that is, positive for HCV RNA; Section 8.2.9).

[36c] HIV infection.

[37] in the opinion of the investigator or sponsor, are unsuitable for inclusion in the study.

5.2.1. Additional Exclusion Criteria for Part C (Patients with AtD)

[38] have syphilis, as shown by positive results for both rapid plasma reagin and Treponema pallidum hemagglutination tests.

[39] are currently experiencing or have a history of other concomitant skin conditions (for example, psoriasis or lupus erythematosus) that would interfere with evaluations of the effect of study medication on AtD.

[40] participants who, in the opinion of the investigator, are currently experiencing or have a history of erythrodermic, refractory, or unstable skin disease that requires frequent hospitalizations and/or IV treatment for skin infections that may interfere with participation in the study.

[41] a history of eczema herpeticum within 12 months prior to screening.

[42] a history of 2 or more episodes of eczema herpeticum in the past.

[43] participants who are currently experiencing a skin infection that requires treatment, or is currently being treated, with topical or systemic antibiotics.

Note: Participants may not be rescreened until at least 4 weeks after the date of their previous screen failure and at least 2 weeks after resolution of the infection.

[44] have any serious concomitant illness that is anticipated to require the use of systemic corticosteroids or otherwise interfere with study participation or require active frequent monitoring (for example, unstable chronic asthma).

[45] have been treated with the following therapies:

[45a] mAb (for example, ustekinumab, omalizumab, dupilumab, and other experimental biologic agents including lebrikizumab) within 5 half-lives prior to randomization (Visit 2).

[45b] received any parenteral corticosteroid administered by intramuscular or IV injection within 2 weeks prior to study entry (Visit 1) or within 6 weeks prior to planned randomization (Visit 2) or are anticipated to require parenteral injection of corticosteroids during the study.

[45c] have had an intraarticular corticosteroid injection within 2 weeks prior to study entry (Visit 1) or within 6 weeks prior to planned randomization (Visit 2).

Note: Intranasal or inhaled steroid use is allowed during the trial.

[46] have received the following excluded medications/treatments within 4 weeks prior to randomization (Visit 2) or plan to use during the study:

[46a] oral systemic corticosteroids and leukotriene inhibitors.

[46b] systemic immunomodulators including, but not limited to, cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, and Janus kinase inhibitors (tofacitinib and ruxolitinib).

[46c] sedating antihistamines including, but not limited to, alimemazine, chlorphenamine, clemastine, cyproheptadine, diphenhydramine, hydroxyzine, ketotifen, and promethazine.

Note: Participants may use newer, less sedating antihistamines (for example, fexofenadine, loratadine, and cetirizine).

[46d] any other systemic therapy used to treat AtD or symptoms of AtD (approved or off-label use).

[46e] phototherapy, including therapeutic phototherapy (psoralen plus ultraviolet-A, and ultraviolet-B), excimer laser, or tanning beds.

[47] patients with a positive beta-D-glucan test at screening and a confirmed diagnosis of pneumocystis pneumonia will be excluded.

[48] women who are lactating.

[49] have experienced hypersensitivity to the active substance or to any of the excipients

[50] have evidence of, or a positive test for, HBV infection defined as:

[50a] positive for hepatitis B surface antigen (HBsAg), or

[50b] positive for hepatitis B core antibody (HBcAb) and positive HBV DNA, or

[50c] positive for hepatitis B surface antibody (HBsAb) and positive for HBV DNA.

Note: Patients who are positive for HBcAb or HBsAb and negative for HBV DNA may be enrolled in Part C of the study. In this case, repeat testing for HBV DNA is required at least once every month during the study.

5.3. Lifestyle Considerations

Throughout the study, participants must adhere to lifestyle restrictions as outlined by the CRU and in the study procedures. Participants may undergo medical assessments and review of compliance with requirements before continuing in the study.

5.3.1. Meals and Dietary Restrictions

Participants will be required to fast approximately 4 hours before study intervention administration. Water is permitted.

Participants may eat approximately 2 hours postdose. A normal diet may be consumed at all other times during the study.

5.3.1.1. Meals and Dietary Restrictions for Part C

Participants will be required to fast approximately 10 hours before visits that include clinical chemistry testing. Water is permitted.

5.3.2. Substance Use: Caffeine, Alcohol, and Tobacco

- Consumption of caffeine-containing beverages is permitted during the study.
- Participants should not consume alcohol for at least 24 hours prior to dosing and 2 days postdose. During outpatient periods, all participants should be advised to limit alcohol consumption to no more than 2 units per day.
- Participants should be willing and able to abide by smoking restrictions at the CRU during both, the inpatient period and outpatient visits.
- Study participants should be instructed not to donate blood, blood products, and/or tissue during the study or for [redacted] weeks following the study.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomly assigned to study intervention or enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

As SAD Part A and MAD Part B are healthy participant-only studies, individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened, although screening tests such as clinical laboratory tests and vital signs or ECGs may be repeated at the discretion of the investigator. If subjects have minor deviations in screening assessments (for example, vital signs) these may be repeated at the investigator's discretion to confirm eligibility.

As, repeat-dose Part C participants are patients with AtD, individuals who do not meet eligibility criteria for participation in this study (screen failure) may not be rescreened until at least [redacted] weeks after the date of their previous screen failure and at least [redacted] weeks after resolution of a skin infection unless the rescreening is for administrative reasons (see below). Blood tests may be repeated at the discretion of the investigator during screening without being considered a screen failure. Participants may be rescreened 1 time. When rescreening is performed, the individual must sign a new ICF and will be assigned a new identification number.

Allowed rescreening for administrative reasons

An individual may be rescreened once for an administrative reason such as falling out of the screening window because of scheduling conflicts. The sponsor does not need to approve rescreening for an administrative reason. The rescreening can start immediately after the administrative reason has been resolved.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/ Administration of Study Intervention of a Participant

Not applicable.

6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to/used by a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Intervention Name	LY3844583 SC	LY3844583 IV	Placebo SC	Placebo IV
Dosage Level(s)	CCI mg/mL in a CCI solution CCI mg to CCI mg	CCI mg/mL in a CCI solution CCI mg and CCI mg	0.9% sodium chloride solution	0.9% sodium chloride solution
Route of Administration	SC injection	IV infusion	SC injection	IV infusion

Abbreviations: IV = intravenous; SC = subcutaneous.

Packaging and labeling

Study interventions will be supplied by the sponsor in accordance with current Good Manufacturing Practice. Commercially available 0.9% sodium chloride solution will be sourced centrally by the sponsor or by the study site. Study interventions will be labeled as appropriate for country requirements.

6.1.1. Administration Details

In IV dosing cohorts as shown in Section 1.2, the study intervention will be administered as a slow IV infusion over approximately 30 to 75 minutes. Resuscitation equipment, emergency drugs, and appropriately trained staff must be available while the participant is staying at the investigator site.

In SC dosing cohorts as shown in Section 1.2, injections will be administered into the SC tissue of the abdominal wall. Whenever possible, study intervention administration should be carried out by the same personnel.

6.1.2. Premedication for Infusions

Premedication for the infusions is not planned. However, if an infusion reaction occurs, appropriate medication may be used as determined by the study investigator. If infusion reactions are observed but review of the data suggests that dose escalation may continue, administration of acetaminophen 500 to 1000 mg and/or an antihistamine may be administered orally 30 to 60 minutes prior to the start of infusion for subsequent participants.

The decision to implement premedication for infusions in subsequent cohorts will be made by the investigator and sponsor and recorded in the study documentation, along with the dose-escalation decision.

Any premedications given will be documented as a concomitant therapy (Section 6.8).

6.1.3. Management of Infusion Reactions

There is a risk of infusion reaction with any biological agent; therefore, all participants should be monitored closely.

Symptoms and signs that may occur as part of an infusion reaction include, but are not limited to

- fever
- chills
- nausea
- headache
- bronchospasm
- hypotension
- angioedema
- throat irritation
- rash
- pruritus
- myalgia, and
- dizziness.

In the event that a significant infusion reaction occurs, the following guidance should be followed:

- The infusion of the study intervention should be slowed. For example, reduce infusion rate by 50%, that is, an infusion rate of 12 mL/hour becomes 6 mL/hour or slower. The infusion can also be stopped, depending on the symptoms or signs present.
    - If slowed, the infusion should be completed at the slower rate, as tolerated.
    - If determined by the investigator that the infusion should no longer continue, no further attempts to dose the participant should be made.
- Supportive care should be employed in accordance with the symptoms or signs.
- If a participant's infusion reaction is sufficiently severe to discontinue the infusion,
    - subsequent infusions may be administered with premedication at the discretion of the investigator following agreement with the sponsor.
- If a participant's infusion rate is reduced due to an infusion reaction,
    - subsequent infusions may be administered at the discretion of the investigator following agreement with the sponsor
    - the infusion rate of the subsequent infusions must not exceed the slowest rate used to complete the infusion in the event of an infusion reaction, and
    - premedication may be administered at the discretion of the investigator in consultation with the sponsor.
- If it is determined the participant should not receive further doses of study intervention, the participant should complete AE and other follow-up procedures per Section 1.3 of this protocol.

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.
3. The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual
5. Study intervention will be prepared by an unblinded pharmacy staff or pharmacist who is not involved in any other study-related procedures

6.3. Measures to Minimize Bias: Randomization and Blinding

On Day [redacted] participants will be assigned a unique number (randomization number). The randomization number encodes the participant's assignment to the study, according to the randomization schedule. Each participant will be dispensed study intervention labeled with his/her unique randomization number throughout the study. Participants will be sequentially enrolled to cohorts. Within the following cohorts, participants will be randomized to receive LY3844583 or placebo as described in Section 4.1.

Blinded study with unblinded site pharmacist who is dispensing drug	Participants will be randomized to receive LY3844583 or placebo as described in Section 4.1. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. To maintain this blind, an otherwise uninvolved third party will be responsible for the reconstitution and dispensation of all study intervention and will endeavor to ensure that there are no differences in time taken to dispense following randomization. In the event of a quality assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization or dispensing has been done accurately.

Blinding will be maintained throughout the conduct of the study as described in the Statistical Analysis Plan.

For Parts A and B of the study, emergency codes will be available to the investigator. A code, which reveals the treatment group for a specific study participant, may be opened during the study only if the participant's well-being requires knowledge of the participant's treatment assignment.

For Part C of the study, emergency unblinding for AEs may be performed through the interactive web-response system, which may supplement or take the place of emergency codes generated by a computer drug labeling system. This option may be used ONLY if the participant's well-being requires knowledge of the participant's treatment assignment. All actions resulting in an unblinding event are recorded and reported by the interactive web-response system.

If a participant's study treatment assignment is unblinded, the participant must be discontinued from the study, unless the investigator obtains specific approval from the sponsor for the study participant to continue in the study. During the study, emergency unblinding should occur only by accessing the study participant's emergency code.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted for medical management of the event. The participant's safety must always be the first consideration in making such a determination. Where feasible and when timing of the emergent situation permits, the investigator should attempt to contact the Lilly medical monitor before unblinding a participant's treatment assignment. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible. If a participant's study treatment assignment is unblinded, the participant must be discontinued from the study, unless the investigator obtains specific approval from the sponsor for the study participant to continue in the study. During the study, emergency unblinding should occur only by accessing the study participant's emergency code.

Upon completion of the study, all codes must be returned to Lilly or its designee.

6.4. Study Intervention Compliance

Study intervention will be administered under medical supervision by the investigator or designee. The dose of study intervention and study participant identification will be confirmed prior to the time of dosing. The date and time of each dose administered will be recorded in the source documents and will be provided to the sponsor as requested.

6.5. Dose Modification

Prior to dose escalation, a SRC meeting will be undertaken by the sponsor (who may be unblinded) and the investigator (blinded) to evaluate the safety data and agree on the appropriate dose for the next cohort. The SRC will consist of at least the Principal Investigator or designee responsible for the clinical follow-up of the previous cohort, a medical representative, and Lilly's Clinical Pharmacologist. Any available CCI exploratory data, and PK data may be used to inform dose selection for the dose levels in the SAD and MAD, but these data are not required for dose escalation.

In the event that exposure in the SAD or MAD cohorts, at a given dose level, is lower or higher than predicted, the

- subsequent dose level in the SAD or MAD cohorts may be adjusted to target the exposures in Table KKAA.2 using the emerging PK data.
- dose frequency for the Parts B and C may be adjusted to no more than CCI administration using the emerging PK data.

If considered appropriate, previous dose levels may be repeated and the follow-up period may be modified and/or extended based on emerging data. In addition, PK, CCI and exploratory data collection time points may be modified and/or removed based on emerging data.

The planned dose levels, route of administration, and the distribution of Japanese, Chinese, and non-Japanese and/or non-Chinese participants may be modified based on emerging data collected during the study.

Since these adjustments are allowable changes permitted by the protocol, a protocol amendment is not required.

6.5.1. Dose Decision/Escalation

By nature of being a dose-escalation study, data will be evaluated on an ongoing basis.

Safety data, in particular AEs, SAEs, and laboratory abnormalities, will be independently assessed by the investigator.

Safety and tolerability data will be the primary criteria for the dose escalation in the SAD and MAD Part B (Sections 8.2). It is planned to review available PK data in the following instances:

- PK from at least SAD Cohort 1 and any other SAD cohorts for the dose decision to SAD Cohort 4.
- PK from at least SAD Cohort 4 and any other SAD cohorts for the dose decision to MAD Part B Cohort 1.
- PK from at least SAD Cohort 5 and any other SAD cohorts for the dose decision to optional SAD Cohorts 6 and 7.
- PK from at least SAD Cohort 5 and any prior SAD and MAD Part B Cohort 1 for the dose decision to Part C.

The PK results, CCI and exploratory data may be used as supporting data for dose escalation, but such data are not required for each dose decision.

After review of these data, an agreement on the appropriate dose will be made by the investigator and sponsor for the next cohort/dose level. The magnitude of dose escalations may be reduced following data review, but subsequent escalations should not be increased by more than approximately CCI to CCI, relative to the dose in the previous cohort.

No dose decision can occur without prior discussion and agreement between the investigators and the sponsor.

6.5.1.1. Single-ascending Dose Escalation

Dose escalation will be as follows:

- The decision to dose the remaining participants in Cohort 1 and the sentinel pair in Cohort 2 will occur when at least CCI days have elapsed after the Cohort 1 sentinel pair have been dosed, and after review of safety and tolerability data from at least CCI days post-administration.
    - The rationale to escalate from Cohort 1 to Cohort 2 is based on providing adequate safety and tolerability decision-making information for sufficient

duration post-administration, as well as the large projected exposure multiples for Cohort 3 (Section 4.3).

- The decision to dose the remaining participants in Cohort 2 will occur when at least [redacted] days have elapsed after the Cohort 2 sentinel pair have been dosed, and after review of safety and tolerability data from at least [redacted] days post-administration.
- The decision to escalate to Cohorts 3 and 4 will occur when at least [redacted] days have elapsed after the remaining participants in Cohort 2 have been dosed, and after review of safety and tolerability data from at least [redacted] days post-administration from at least [redacted] participants from Cohorts 1 and 2 each. If available, emerging PK and [redacted] data from Cohorts 1 and 2 may also be considered in dose decisions or escalations for Cohorts 3 and 4.
    - The rationale to escalate from Cohort 2 to Cohorts 3 and 4 concurrently is based on providing adequate safety and tolerability decision-making information for sufficient duration post-administration as well as the large projected exposure multiples for Cohorts 3 and 4 (Section 4.3). Additionally, participants in Cohort 4 will be dosed in sequence, each following, at a minimum, completion of the administration for the prior participant.
- The decision to escalate to Cohort 5 will occur after review of safety and tolerability data from at least [redacted] days post-administration of at least [redacted] participants in SAD Cohorts 3 and 4 each, along with all available PK data from SAD Cohorts1 and 2. Emerging [redacted] data from Cohorts 1 and 2 may also be considered in dose decisions or escalations for Cohort 5.
    - The rationale to escalate from Cohort 4 to Cohort 5 is based on providing adequate safety and tolerability decision-making information for a sufficient duration post-administration as well as on a maximum anticipated exposure increase of no greater than approximately [redacted] to [redacted] in Cohort 5. Additionally, participants in Cohort 5 will be dosed in sequence, each following, at a minimum, completion of the administration for the prior participant.
- Safety, tolerability, and PK data from SAD Cohort 5 and any other available PK and [redacted] data from lower dose SAD cohorts will be reviewed prior to conducting optional Cohorts 6 and 7.

6.5.1.2. Multiple-ascending dose Part B Escalation

The highest dose in the Part B of the study will not exceed the maximum dose administered in the SAD portion.

For Part B Cohort 1, available PK data from SAD Cohort 4 will be reviewed along with at least [redacted]-day post-administration safety and tolerability data from SAD Cohorts 3 and 4 prior to initiating MAD Cohort 1.

Safety and tolerability data will be the primary criteria for dose-escalation decision from MAD Part B Cohort 1 to Cohort 2. Available PK data from any prior SAD cohorts will be reviewed along with [redacted]-day post the last administration safety and tolerability data from Part B Cohort 1,

and SAD Cohort 5 have been collected from at least [redacted] participants from each cohort prior to beginning Part B Cohort 2.

Assuming there are no safety concerns, a provisional decision to escalate to the next dose level will be made. However, dose escalation will not occur until the participants in the MAD Cohort 1 have been assessed on the day of the [redacted] dose and are deemed eligible to receive their final dose.

6.5.1.3. Repeat-dose Part C Escalation

The highest dose in Part C of the study will not exceed the maximum dose administered in the SAD portion.

Prior to beginning Part C, the following data will be reviewed:

- any available PK data from SAD Cohort 5 (and other SAD cohorts)
- [redacted]-day post administration safety and tolerability data up to and including the SAD Cohort 5, and
- [redacted]-day post the last administration safety and tolerability data from Part B Cohort 1.

6.6. Continued Access to Study Intervention after the End of the Study

LY3844583 will not be made available after conclusion of the study to patients.

6.7. Treatment of Overdose

For this study, an overdose of LY3844583 is considered any dose higher than the dose assigned through randomization. Treatment for overdose is best supportive care.

The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should

- contact the Lilly Clinical Pharmacologist immediately
- evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or the dose should be reduced.
- closely monitor the participant for any AE/SAE and laboratory abnormalities, for approximately 12 weeks or 5 half-lives (whichever is longer).
- obtain a blood sample for PK analysis if requested by the Lilly Clinical Pharmacologist (determined on a case-by-case basis), and
- document the quantity of the excess dose as well as the duration of the overdose in the CRF.

6.8. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with

- reason for use

- dates of administration including start and end dates, and
- dosage information including dose and frequency for concomitant therapy of special interest.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

In general, concomitant medication should be avoided. Use of chronic, stable doses of thyroid hormone, or hormone replacement therapy is allowed. Acetaminophen (1 g, maximum 4 g/24 hours) may be administered at the discretion of the investigator for treatment of headaches and so on. Antihistamine may be administered as premedication for infusion at the discretion of the investigator. If the need for concomitant medication (other than acetaminophen) arises, inclusion or continuation of the participant may be at the discretion of the investigator after consultation with the sponsor. Any medication used during the course of the study must be documented.

For AtD therapies permitted as part of rescue therapy see below.

Criteria for rescue therapy initiation

- Investigators should attempt to manage participants with emollients; however, investigators are allowed to rescue participants who are experiencing unacceptable or worsening symptoms of AtD at Week [redacted] Prior to rescue, it is recommended that increased frequency of emollient use is attempted to at least twice a day or more in an effort to control symptoms. The rationale for rescue will be documented.

Choice of rescue therapy treatment

- Triamcinolone 0.1% cream and/or hydrocortisone 2.5% ointment. In the event, where providing 1 or both of these topical formulations is not possible, an alternate, equivalent potency TCS cream and/or ointment may be provided.
    - Commercially available triamcinolone 0.1% cream and/or hydrocortisone 2.5% ointment may be supplied by the clinical site. Where providing triamcinolone 0.1% cream and/or hydrocortisone 2.5% ointment is not possible, an equivalent potency TCS cream and/or ointment that is in line with local practices can be supplied.
    - TCS cream and/or ointment that is of appropriate potency and in line with local practices can be supplied by the clinical site.
- Investigators may elect to use TCNIs and/or crisaborole where approved, although use of either of them during the study is not encouraged. If TCNIs are prescribed, use should be limited to problem areas only (for example, face, neck, skin folds, and genital areas).
- On the days of study visits, topical therapy should not be applied before the participant has undergone all study procedures and clinical evaluations in order to allow adequate assessment of skin dryness.
- Participants receiving topical therapy will remain on the study and continue to take IP. Use of rescue therapy will be documented in the eCRF.

In participants who do not improve sufficiently with the provided rescue topical therapy after 7 days, a higher potency TCS may be used and IP may continue. It is recommended that if a

participant achieves “clear” to “almost clear” skin after topical rescue, medium- and/or high-potency TCSs and TCNIs should be stopped, and low-potency TCSs (for example, hydrocortisone 2.5% ointment) should be used once daily for an additional 7 days, then stopped. If lesions return, participants can be retreated with TCSs with or without TCNIs and/or crisaborole as before at the discretion of the investigator.

If topical rescue therapy as described above fails to sufficiently control AtD symptoms, then oral systemic medications may be used as rescue (for example, corticosteroids, cyclosporine, and methotrexate); however, IP will be required to be permanently discontinued for the remainder of the [redacted]-week study duration. If these medications are needed for other medical conditions (for example, asthma flare), they will still be treated as rescue medications.

Investigators should make every attempt to conduct efficacy and safety assessments immediately before administering any rescue treatment. An unscheduled visit can be used for this purpose if necessary.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Participants discontinuing from study intervention prematurely for any reason should complete AE and other follow-up procedures per Section 1.3 of this protocol.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1).

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study for additional data collection consistent with routine safety monitoring. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

The following infections lead to study intervention discontinuation: confirmed diagnosis of pneumocystis pneumonia, HIV, and active TB. Also, hepatitis B and C (as further described in Section 7.1.2).

7.1.1. Rules for Stopping Dosing and Enrollment in a Cohort

If any of the following scenarios occur, dosing at the current level and further dose escalation will be interrupted and may resume only following written approval from the sponsor medical monitor:

- A single participant experiences an SAE unless obviously unrelated to LY3844583 administration.
- Two or more participants per cohort develop TEAEs or clinically significant changes in laboratory safety that are graded as at least moderate, unless there is an obvious explanation other than study intervention or study procedures for the event(s).
- One or more participants present severe AEs related to IV infusion that are considered to be related to LY3844583 and the TEAE does not resolve with a reduced IV infusion rate or supportive care.

7.1.2. Liver Chemistry Stopping Criteria

The study drug should be interrupted or discontinued if 1 or more of these conditions occur.

Elevation	Exception
ALT or AST >5x ULN	
ALT or AST >3x ULN and either TBL >2x ULN or INR >1.5	In participants with Gilbert's syndrome, doubling of direct bilirubin should be used for drug interruption or discontinuation decisions rather than TBL >2x ULN.
ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >3x ULN (when the source of increased ALP is the liver)	
ALP >2.5x ULN and TBL >2x ULN	In participants with Gilbert's syndrome, doubling of direct bilirubin should be used for drug interruption or discontinuation decisions rather than TBL >2x ULN.
ALP >2.5x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	

Abbreviations: ALP = alkaline phosphatase, ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin level; ULN = upper limit of normal

Source: FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009 and other consensus guidelines with minor modifications.

Resumption of the study drug can be considered only in consultation with the Lilly-designated medical monitor and only if liver test results return to approximately baseline and if a self-limited nondrug etiology is identified.

7.1.3. Discontinuation related to Hepatitis B Virus

If HBV DNA is detected, study intervention will be permanently discontinued, and the participant should receive appropriate follow-up medical care.

7.1.4. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant may withdraw from the study

- at any time at the participant's own request
- at the request of the participant's designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if enrolled in any other clinical study involving an IP or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study

- if the participant, for any reason, requires treatment with a therapeutic agent that is prohibited by the protocol and has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.

At the time of discontinuing from the study, if possible, the participant will complete procedures for an early discontinuation visit as shown in the SoA (Section 1.3). If the participant has not already discontinued the study intervention, the participant will be permanently discontinued from the study intervention at the time of the decision to discontinue the study.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.1.5. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly clinical pharmacologist and the investigator to determine if the participant may continue in the study. If both agree that it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor to allow the inadvertently enrolled participant to continue in the study with or without continued treatment with IP.

7.2. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel or designee are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Section 1.3 lists the SoA, detailing the study procedures and their timing (including tolerance limits for timing). The specifications in this protocol for the timings of safety and sample collection are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based on emerging clinical information. The scheduled time points may be subject to minor alterations; however, the actual time must be correctly recorded in the CRF.
- Appendix 2 (Section 10.2) lists the laboratory tests that will be performed for this study.
- Appendix 2 (Section 10.2.1) provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.
- Unless otherwise stated in subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.
- Failure or delays that is outside stipulated time allowances in performing procedures or obtaining samples due to legitimate clinical issues (e.g. equipment technical problems, venous access difficulty, or subject defaulting or turning up late on an agreed scheduled procedure) will not be considered as protocol deviations, but the CRU will still be required to notify the sponsor.

8.1. Efficacy Assessments

In Part C of the trial, the following efficacy assessments will be performed:

Clinician-rated scales

- ***Validated Investigator's Global Assessment for Atopic Dermatitis (vIGA-AD):*** The vIGA-AD measures the investigator's global assessment of the participant's overall severity of their AtD, based on a static, numeric 5-point scale from 0 (clear skin) to 4 (severe disease). The score is based on an overall assessment of the degree of erythema, papulation/induration, oozing/crusting, and lichenification.

- ***Eczema Area and Severity Index (EASI):*** The EASI assesses 4 clinical signs of disease, each on a 0 to 3 scale: (1) erythema, (2) induration/papulation, (3) excoriation, and (4) lichenification. Scores range from 0 to 72. The EASI evaluates 2 dimensions of AtD: disease extent and clinical signs. Body surface area affected by AtD will be derived from data collected as part of the EASI assessment.
- ***SCORing Atopic Dermatitis (SCORAD):*** The SCORAD index assesses: 1) 6 clinical signs of disease, each on a 0 to 3 scale, 2) extent of involved surface area, up to 100%, and 3) subjective evaluations of itch and sleeplessness, each on a 0 to 10 scale. Scores range from 0 to 103.

Participant-rated scales

- ***Dermatology Life Quality Index (DLQI):*** The DLQI is a 10-item questionnaire that covers 6 domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. The recall period for this scale is over the "last week." Response categories include "a little," "a lot," and "very much," with corresponding scores of 1, 2, and 3, respectively, and "not at all" or unanswered ("not relevant") responses scored as 0. Scores range from 0 to 30, with higher scores indicating greater impairment of quality of life. A DLQI total score of 0 or 1 is considered to indicate no effect on a participant's health-related quality of life, and a 4-point change from baseline is considered the minimal clinically important difference threshold.
- ***Itch Numeric Rating Scale (NRS):*** The Itch NRS is a patient-administered, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no itch" and 10 representing "worst itch imaginable." Overall severity of a patient's itching is indicated by selecting the number that best describes the worst level of itching in the past 24 hours (Naegeli et al 2015; Kimball et al. 2016).
- ***Patient-Oriented Eczema Measure (POEM):*** The POEM assesses the frequency of 7 symptoms (itching, sleep disturbance, bleeding, weeping/oozing, cracking, flaking, and dryness/roughness) over the last week. Response categories include "No days," "1 to2 days," "3 to4 days," "5 to6 days," and "Every day," with corresponding scores of 0, 1, 2, 3, and 4, respectively. Scores range from 0 to 28, with higher total scores indicating greater disease severity

Evaluation of skin images

CCI

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, skin, lymph nodes, and neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- For each participant, vital signs measurements should be conducted according to the SoA (Section 1.3) and follow the study-specific recommendations included in Manual of Operations for the study.
- Blood pressure and PR should be measured after resting for at least 5 minutes in a supine position.
- Temperature and oxygen saturation will be measured.
- In the case of AEs suggestive for orthostatic measurements, participants should be in a supine position for at least 5 minutes and stand for at least 2 minutes.
- If the participant is unable to stand, supine vital signs only will be recorded.
- Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Additional vital signs may be measured during each study period if warranted.
- Additional vital signs may be measured during each study period if warranted and agreed upon between the investigator and sponsor.

8.2.3. Electrocardiograms

For each participant, ECGs should be collected according to the SoA (Section 1.3).

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the subject receives the first dose of the study intervention should be reported to Lilly, or its designee, as an AE via eCRF.

For each participant in the SAD cohorts, a single or triplicate 12-lead digital ECG will be collected according to the SoA (Section 1.3). For participants in the MAD cohorts, a single ECG will be collected locally and stored at the investigator's site unless the ECG values for participants in SAD cohorts show clinically significant changes (for example, increase in PR or QT interval). In this situation, triplicate 12-lead digital ECGs will be collected for participants in MAD cohorts.

When scheduled at the same time point, ECGs must be recorded before collecting any blood samples. Participants must be in a supine position for at least 5 minutes before ECG collection and remain supine but awake during ECG collection. Consecutive replicate ECGs will be obtained at approximately 1-minute intervals. ECGs may be obtained at additional times, when deemed clinically necessary.

ECGs will be interpreted by a qualified physician (the investigator or qualified designee) at the site soon after the time of ECG collection as possible, and ideally while the subject is still present, to determine whether the subject meets entry criteria at the relevant visit(s) and for immediate subject management, should any clinically relevant findings be identified.

If a clinically significant quantitative or qualitative change from baseline is identified after enrollment, the investigator will assess the subject for symptoms (for example, palpitations, near syncope, and syncope) to determine whether the participant can continue in the study. The investigator or qualified designee is responsible for determining if any change in subject management is needed and must document his/her review of the ECG printed at the time of evaluation from at least 1 of the replicate ECGs from each time point.

Triplicate digital ECGs will be electronically transmitted to a central ECG laboratory designated by Lilly. The central ECG laboratory will perform a basic quality control check (for example, demographics and study details) then store the ECGs in a database. At a future time, the stored ECG data may be overread at the central ECG laboratory for further evaluation of machine-read measurements or to meet regulatory requirements.

The machine-read ECG intervals and heart rate may be used for data analysis and report writing purposes unless a cardiologist overread of the ECGs is conducted prior to completion of the final study report (in which case the overread data would be used).

8.2.4. Clinical Safety Laboratory Tests

- See Section 10.2 (Appendix 2) for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.
- The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a source document agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within the follow-up after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Section 10.2 (Appendix 2), must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.

- If laboratory values from nonprotocol specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator (for example, SAE or AE or dose modification), then report the information as an AE.

8.2.5. Injection-site Reactions

8.2.5.1. Local Injection-site Reaction Assessment following Subcutaneous Administration

- Symptoms of a local ISR may include erythema, induration, pain, pruritus, and edema.
- Injection-site assessments using ISR observational form and CCI [redacted]
- Pain measurements will be quantified using the 100-mm validated pain Visual Analog Scale for all participants, only if injection-site pain is reported.
    - The Visual Analog Scale is a well-validated tool to assess injection-site pain; it is presented as a 100-mm line anchored by verbal descriptors, usually “no pain” and “worst possible pain” (Williamson and Hoggart 2005).
    - The participant will be required to rate any pain at the injection site on a scale of 0 to 100 mm on the line immediately (within 1 minute) following the injection and at the time points listed in the SoA (Section 1.3).
- ISRs, whether recorded as a result of the pre-specified assessment or spontaneously reported reactions, will be recorded as AEs only if they qualify as serious AEs.
- Both prespecified and spontaneously reported injection-site findings (including erythema, induration, pruritus, and edema) will be captured on an ISR observational form as well as CCI [redacted].

8.2.5.2. Injection-site Bleeding Assessment

All injection sites will be observed within 1 minute after each injection by the investigator or designee, and the presence of visible bleeding will be recorded on the eCRF (Injection Procedure Evaluation Form).

A bandage may be placed on the injection site after assessment. In addition, if pain is present, participants will be asked if they can distinguish the cause of the pain (i.e, needle insertion or fluid injection).

8.2.5.3. Injection-site Bruising Assessment

Any spontaneously reported or clinically significant finding of injection-site bruising, as deemed by the Principal Investigator or designee, will be reported as an AE with additional information about the bruise (for example, maximum width).

8.2.6. Safety Monitoring

The sponsor will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The sponsor will periodically review

- trends in safety data
- laboratory analytes, and
- AEs.

When appropriate, the sponsor will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist.

8.2.6.1. Hepatic Safety

Details are provided in Section 10.6 (Appendix 6).

8.2.6.2. Other Safety Monitoring

The sponsor will monitor safety data throughout the course of the study. Lilly will review SAEs within time frames mandated by company procedures.

The sponsor will periodically review the following data:

- trends in safety data, and
- laboratory analytes including hematology and chemistry.

When appropriate, the sponsor will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research physician.

8.2.6.2.1. *Pregnancy Testing*

In this study, a serum pregnancy test will be conducted at screening only. Urine pregnancy test will be used at all other time points. For women who are considered to be not of childbearing potential, follicle-stimulating hormone should be drawn to confirm status as defined in Inclusion Criterion [1b] and to be considered exempt for further pregnancy tests during the study.

8.2.6.2.2. *Infusion-related Reactions*

IRR are systemic events temporally related to infusion (for example, IV or large volume SC) of a therapeutic agent for which an etiology is yet to be identified. IRRs may encompass a wide range of clinical events, including anaphylaxis and other events that may not be directly related to antibody responses, such as CRS

When LY3844583 is used via IV, signs and symptoms of IRR shall be captured in the eCRF.

8.2.6.2.3. *Hypersensitivity*

Many drugs, but particularly biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional data describing each symptom should be provided to the sponsor in the eCRF.

Sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving the study drug. It is recommended that

participants who experience a systemic hypersensitivity reaction be treated per the local standard of care.

In case of systemic hypersensitivity reactions, defined as anaphylaxis or generalized urticaria, additional blood samples should be collected as described in Appendix 2 (Section 10.2 and Section 10.2.1). Laboratory results are provided to the sponsor via the central laboratory.

8.2.7. Immunological Status Assessments

As LY3844583 will be administered for the first time in human subjects, WBC subpopulations (including, but not limited to, total B cells, total T cells, and NK cells) in blood samples collected at visits and times specified in Section 1.3 will be measured using flow cytometry as part of immunophenotyping assessment. A maximum of 3 samples may be collected at additional time points during the study (as unscheduled samples) if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and 24-hour clock time of each sampling will be recorded. Immunoglobulin samples will also be collected as specified in Section 1.3 as part of safety assessment.

8.2.8. Hepatitis B Testing and Monitoring

Testing

Testing for HBV infection includes HBsAg and anti-HBc.

- If HBsAg is positive, the participant is excluded.
- If HBsAg is negative and anti-HBc is negative, the participant is not excluded.
- If HBsAg is negative and anti-HBc is positive, further testing for HBV DNA is required.
    - If the screening HBV DNA is positive, the participant is excluded.
    - If the screening HBV DNA is negative, the participant is not excluded.

Monitoring

If the screening HBV DNA is negative, and proof of HBV vaccination cannot be provided, repeat testing for HBV DNA is required at least every 3 months during the study.

8.2.9. Hepatitis C Testing

Testing for HCV infection includes anti-HCV.

- If anti-HCV is positive, a test for circulating HCV RNA is required.
    - If HCV RNA test is positive, the participant is excluded.

8.2.10. Pregnancy Testing

In this study, pregnancy testing will be carried out at time points indicated in SoA (Section 1.3).

8.3. Adverse Events, Serious Adverse Events, and Product Complaints

The definitions of the following events can be found in Section 10.3:

- AEs
- SAEs
- PCs

These events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet these definitions and remain responsible for following up events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (Section 7).

Care will be taken not to introduce bias when detecting events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about event occurrences.

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.2). For PCs, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality. Further information on follow-up procedures is provided in Appendix 10.3.

Investigators are responsible for monitoring the safety of participants who have entered this study and for alerting Lilly or its designee to any event that seems unusual even if this event may be considered an unanticipated benefit to the participant.

The investigator is responsible for the appropriate medical care of participants during the study.

Adverse events

Investigators are responsible for monitoring the safety of participants who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject.

The investigator is responsible for the appropriate medical care of participants during the study.

Investigators must document their review of each laboratory safety report. The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the study intervention or the study, or that caused the participant to discontinue the study intervention before completing the study. The participant should be followed up until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator. After the ICF is signed, study-site personnel will record, via eCRF, the occurrence and nature of each participant's preexisting conditions. Additionally, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to the study treatment, or a study procedure, considering the disease, concomitant treatment, or pathologies.

A “reasonable possibility” means that there is a potential cause-and-effect relationship between the IP, study device and/or study procedure, and the AE.

Planned surgeries should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a participant’s study intervention is discontinued as a result of an AE, study-site personnel must report this to Lilly or its designee via eCRF.

Serious adverse events

Study-site personnel must alert the sponsor, or its designee, of any SAE as soon as practically possible.

Additionally, study-site personnel must alert Lilly Global Patient Safety, or its designee, of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed up with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Although all AEs are recorded in the eCRF after signing the informed consent, SAE reporting to the sponsor begins after the participant has signed informed consent and has received the study intervention. However, if an SAE occurs after signing informed consent, but prior to receiving study intervention, AND is considered reasonably possibly related to a study procedure then it must be reported.

Investigators are not obligated to actively seek AEs or SAEs in participants once they have discontinued from and/or completed the study (the subject summary eCRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event reasonably possibly related to the study intervention or study participation, the investigator must promptly notify Lilly.

8.3.1. Timing and Mechanism for Collecting Events

This table describes the timing, deadlines, and mechanism for collecting events.

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Event					
AE	Signing of ICF	Participation in study has ended	As soon as possible upon site awareness	AE eCRF	NA
Serious Adverse Event					
SAE and SAE updates - prior to start of study intervention **and** deemed reasonably possibly related with study procedures	Signing of the ICF	Start of intervention	Within 24 hours of awareness	LSS SAE reporting process	NA
SAE and SAE updates - after start of study intervention	Start of intervention	Participation in study has ended	Within 24 hours of awareness	LSS SAE reporting process	NA
SAE - after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	NA	Promptly	LSS SAE reporting process	NA
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	At least [redacted] weeks for Parts A and B and at least [redacted] weeks for Part C after the last dose	Within 24 hours of learning of the pregnancy	LSS SAE reporting process	SAE paper form

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	Product complaint form	NA
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product complaint form	NA
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed product complaint form with all changes signed and dated by the investigator	NA
PC (if investigator becomes aware)	Participation in study has ended	NA	Promptly	Product complaint form	

Abbreviations: AE = adverse event; eCRF = electronic case report form; ICF = informed consent form; LSS = Lilly safety system; NA = not applicable; PC = product complaint; SAE = serious adverse event.

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive intervention.
- After learning of a pregnancy in the female partner of a study participant, the investigator will
  - obtain a consent to release information from the pregnant female partner directly, and
  - within 24 hours after obtaining this consent will record pregnancy information on the appropriate form and submit it to the sponsor.

The female partner will also be followed up to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, fetal status (presence or absence of anomalies), or indication for the procedure.

Female participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed up to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ≥20 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in protocol Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention. If the participant is discontinued from the study, follow the standard discontinuation process and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

8.3.3. Adverse Events of Special Interest

Not applicable.

8.4. Pharmacokinetics

CCI [redacted] A maximum of 3 additional blood samples may be collected as additional unscheduled time points during the study if warranted and agreed upon between both the investigator and sponsor. Refer to Section 10.2.1 for details.

Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

Drug concentration information that may unblind the study will not be reported to CRU or blinded personnel until the study has been unblinded.

In the event of early discontinuation of a participant, a PK sample will be taken at the early discontinuation visit as an unscheduled sample. The actual date and time of collection must be recorded.

8.4.1. Bioanalytics

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor. Concentrations of will be assayed using a validated enzyme-linked immunosorbent assay method. Analyses of samples collected from placebo-treated participants are not planned.

Bioanalytical samples collected to measure IP concentrations will be retained for a maximum of 1 year following last participant visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses such as, but not limited to, CCI [redacted].

8.5. Pharmacodynamics

At the times specified in the SoA (Section 1.3) venous blood samples will be collected and used to determine the target engagement (CCI effects and effects on immunoglobulins by LY3844583. Blood will be collected in order to evaluate CCI and immunoglobulin activity.

CCI supplies required for the collection and shipment of the participants' samples will be supplied by the sponsor. CCI sample handling and shipment to the central laboratory will occur per instructions given to the study site. The actual date and 24-hour clock time of each CCI sampling will be recorded. Any unused blood samples will be destroyed in accordance with local regulations.

Samples will be analyzed at a laboratory approved by the sponsor using validated assays.

8.6. Genetics

A blood sample will be collected for pharmacogenetic analysis as specified in the SoA (Section 1.3), where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable exposure or response to LY3844583 and to investigate genetic variants thought to play a role in disease. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All samples will be coded with the subject number. These samples and any data generated can be linked back to the participant only by the CRU personnel.

Samples will be retained for a maximum of 15 years after the last participant visit, or for a shorter period if local regulations and/or ERBs impose shorter time limits, for the study at a facility selected by Lilly or its designee. This retention period enables use of new technologies,

response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3844583 or after it is commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome-wide association studies, multiplex assays, and candidate gene studies. Regardless of technology utilized, data generated will be used only for the specific research scope described in this section.

8.7. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of patient/subject response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including DNA, RNA, proteins, lipids, and other cellular elements.

Blood samples for nonpharmacogenetic biomarker research will be collected at the times specified in the SoA (Section 1.3), where local regulations allow. A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor.

Samples will be used for research on the drug target, disease process, variable response to LY3844583, pathways associated with disorders such as multiple sclerosis and/or rheumatoid arthritis, mechanism of action of LY3844583, and/or research method or for validating diagnostic tools or assay(s) related to disorders.

All samples will be coded with the subject number. These samples and any data generated can be linked back to the participant only by the CRU personnel.

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and/or ERBs impose shorter time limits, at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3844583 or after LY3844583 is commercially available.

8.7.1. Skin Biopsies for Participants with Atopic Dermatitis

Participants in Part C may participate in having skin biopsies, which will be collected at the visits shown in the SoA (Section 1.3). Detailed instructions for handling the biopsies at the study site will be provided by the sponsor. These biopsies will be analyzed in relation to the changes in disease activity measures within the same participant with AtD.

Biopsies will be retained for a maximum of 15 years after the last participant visit, or for a shorter period if local regulations and ERBs allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to the IP. Any samples remaining after 15 years will be destroyed.

8.8. Immunogenicity Assessments

At the visits and times specified in the SoA (Section 1.3), venous blood samples will be collected and stored for potential future analysis to determine antibody production against LY3844583. Antibodies may be further characterized for their ability to neutralize the activity of LY3844583. To interpret the results of immunogenicity, a venous blood sample will be collected at the same time points to determine the serum concentrations of LY3844583. All samples for immunogenicity should be taken predose, when applicable and possible

TE-ADAs are defined in Section 9.3.4.4. If the immunogenicity sample at the last scheduled assessment or discontinuation visit is TE-ADA+, additional samples may be taken until the signal returns to baseline (that is, no longer TE-ADA+) or for up to 1 year after the last dose

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and ERBs allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to the IP. Any samples remaining after 15 years will be destroyed

8.9. Health Economics or Medical Resource Utilization and Health Economics

This section is not applicable for this study.

9. Statistical Considerations

The SAP will be finalized prior to the first database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.1. Statistical Hypotheses

No formal hypotheses will be tested for the safety analyses.

9.1.1. Multiplicity Adjustment

Adjustment for multiple comparisons will not be employed in any analysis for this study.

9.2. Populations for Analyses

This table describes the populations planned for use in the analyses. The mITT population, as defined below, will be used in efficacy analyses unless otherwise noted in the SAP:

Population	Description
Enrolled	All participants who sign informed consent.
Intent-to-treat (ITT) (Part C only)	All randomized participants. Participants will be analyzed according to the treatment to which they were assigned (regardless of whether the participant fails to receive the correct treatment, or otherwise fails to follow the protocol).
Modified ITT (mITT) (Part C only)	All randomized participants who receive at least 1 dose of study treatment. Participants will be analyzed according to the treatment to which they were assigned (regardless of whether the participant fails to receive the correct treatment, or otherwise fails to follow the protocol).
Safety	All randomized participations who receive at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received.
PK analysis set	All randomized participants who receive at least 1 dose of the study drug and have evaluable PK data.

Abbreviation: PK = pharmacokinetics.

9.2.1. Study Participant Disposition

A detailed description of participant disposition will be provided at the end of the study, including a summary of the number and percentage of participants entered into the study and randomized, and number and percentage of participants who complete the study or discontinue, both overall and by reason for discontinuation. A summary of important protocol deviations will be provided.

Approved on 08 Jun 2023 GMT

9.2.2. Study Participant Characteristics

Participant demographic characteristics and medical status at baseline (for example, prior therapies and preexisting conditions) will be recorded, listed, and summarized overall and by treatment group using descriptive statistics. Other participant characteristics may be summarized overall and by treatment group as deemed appropriate.

9.2.3. Treatment Compliance

No analyses are planned to assess treatment compliance, given that participants will receive study intervention directly from the investigator or designee at the study site under medical supervision.

9.3. Statistical Analyses

9.3.1. General Considerations

Statistical analyses of this study will be the responsibility of Lilly or its designee.

PK analyses will be conducted on data from all participants who receive at least 1 dose of the study drug and have evaluable PK data.

Safety analyses will be conducted for all enrolled participants whether or not they completed all protocol requirements. Safety analyses will be presented for all participants, separately by race and ethnicity (for example, Japanese and non-Japanese or Chinese and non-Chinese) and separately for healthy participants and patients with AtD.

Summary statistics will describe participant variables at baseline. Continuous variables will be summarized by the number of observations, mean, standard deviation, minimum, median, and maximum values. Categorical variables will be summarized by counts and percentages. Summary statistics will be provided for all participants, separately by population, and separately for healthy participants and patients with AtD as appropriate. No tests to assess statistical significance are planned due to the small sample size per treatment group.

The baseline value is the last available value before the first dose of study intervention.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Study results may be pooled with the results of other studies for safety, PD, and population PK analysis purposes to avoid issues with post-hoc analyses and incomplete disclosures of analyses.

Handling of missing, unused, and spurious data are addressed prospectively in the overall statistical methods described in the protocol and in the SAP, where appropriate. Any change to the data analysis methods or imputation methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the SAP and the clinical study report.

9.3.2. Primary Endpoint

The primary objective for this study is to assess the safety and tolerability following single and multiple doses of LY3844583 in healthy participants and repeat doses of LY3844583 in patients with AtD. The primary endpoint is frequency of TEAEs and SAEs.

Approved on 08 Jun 2023 GMT

All IP and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of symptoms for each treatment will be presented by severity and by association with study drug as perceived by the investigator. Symptoms reported to occur prior to enrollment will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified according to the Medical Dictionary for Regulatory Activities.

The number of participants who experience a TEAE and/or SAE will be summarized by study treatment - both for all causalities and TEAEs/SAEs related to the study drug. All TEAEs will be summarized by system organ class and by decreasing frequency within system organ class.

The number of drug-related SAEs and AEs will be reported.

9.3.3. Pharmacokinetic Analyses

The secondary objective is to characterize the PK after single and multiple SC and IV administrations of LY3844583. The secondary endpoint is C_{max} and AUC.

Pharmacokinetic parameter estimates for LY3844583 will be calculated using standard noncompartmental methods of analysis and summarized by dose using descriptive statistics.

The primary parameters for analysis in Part A and Part B will be C_{max} and AUC after single- and multiple-dose administration. Other noncompartmental parameters such as half-life, apparent clearance, and apparent volume of distribution may be reported. An evaluation of F with consideration of ethnicity or other demographic differences between groups, if considered appropriate, will be performed using SAD Cohorts 3 and 4 data where the same dose is administered both IV and SC. Subgroup comparisons of Japanese versus non-Japanese participants as well as Chinese versus non-Chinese participants may be performed using graphical and tabular comparisons.

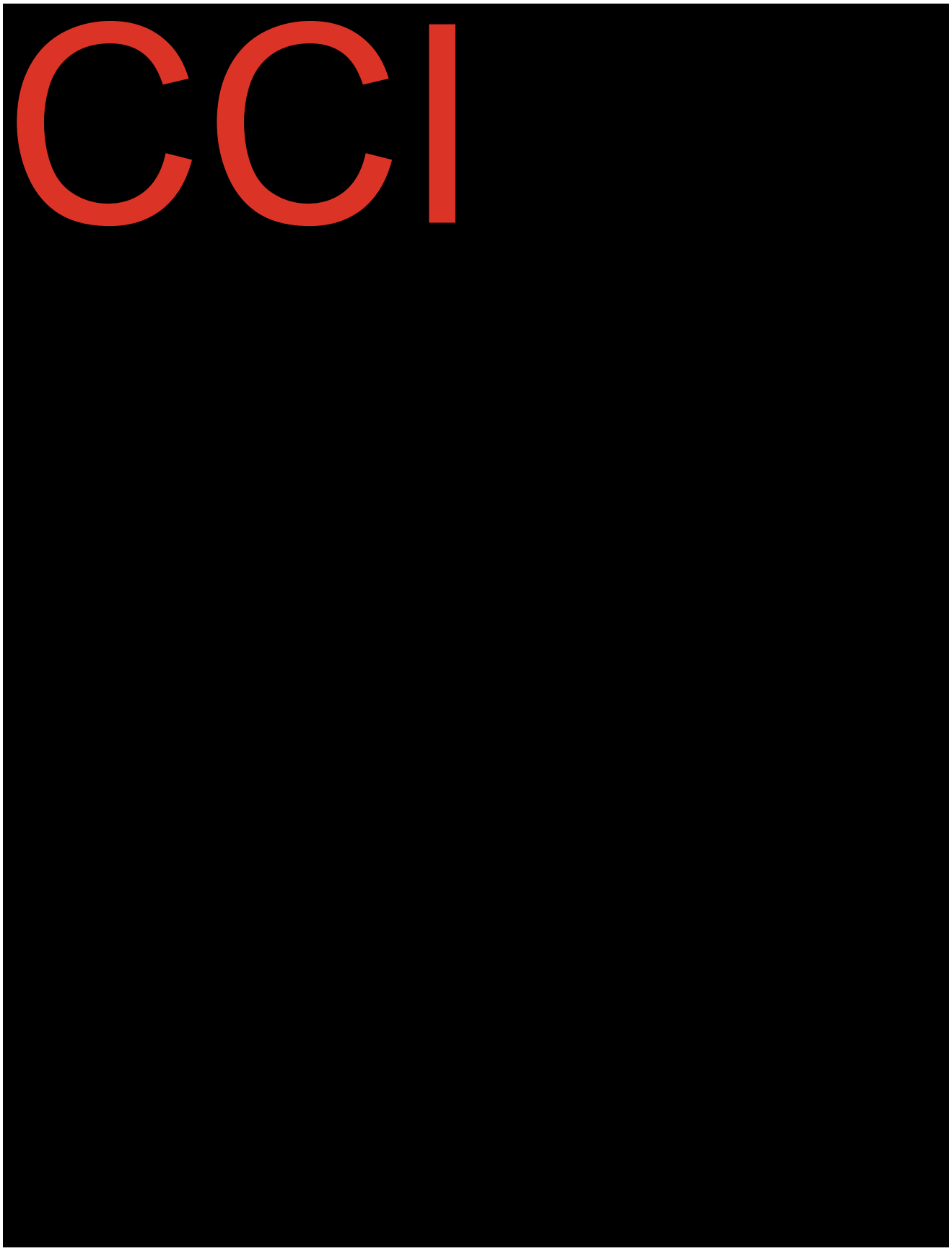
The dose proportionality of selected LY3844583 PK parameters in Part A, including log transformed C_{max} and relevant AUC values, may be examined across the SC and IV dose ranges using a power model approach (Smith et al. 2000) to estimate the slope of the power model, which represents the ratio of dose-normalized geometric means.

For Part C, descriptive statistics will be performed on the trough concentrations due to sparse sampling. If data supports, C_{max} and AUC will be calculated using noncompartmental methods and summarized.

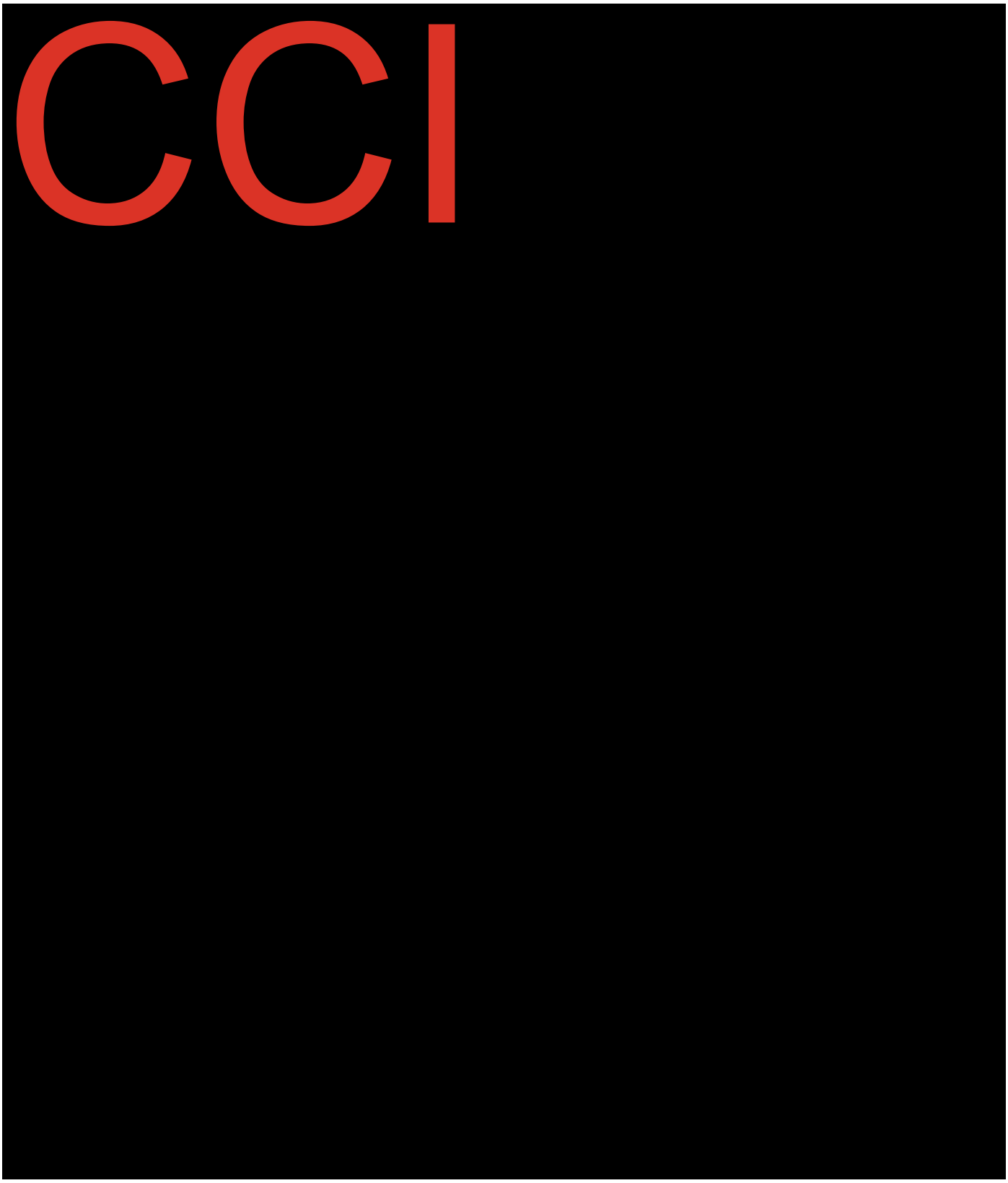
To facilitate the planning for future clinical studies, additional analyses may be conducted as appropriate. The concentration-time data may be analyzed using nonlinear mixed effects modelling approaches if deemed necessary.

9.3.4. Exploratory Endpoints





Approved on 08 Jun 2023 GMT



Approved on 08 Jun 2023 GMT



9.4. Interim Analysis

No formal interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the Lilly clinical pharmacologist, investigator, or designee will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.

9.5. Sample Size Determination

The study will enroll approximately CCI participants (CCI healthy participants and up to CCI patients with AtD). An additional CCI participants in SAD Cohorts 6 and 7 may be enrolled depending on emerging data. For additional details, see Table KKAA.1.

The sample size is customary for Phase 1 studies evaluating safety, tolerability, and PK and is not powered on the basis of any a priori statistical hypothesis testing results. The sample sizes for Parts A and B are not adjusted for potential dropout. The sample size for Part C is adjusted to account for potential dropouts. However, the protocol allows replacement if it is deemed necessary to obtain sufficient data for interpretation.

For purposes of this study, a subject completes the study when all scheduled procedures shown in the SoA have been finished. Subjects who withdraw before completing all dosing administrations may be replaced. Replacement subjects will complete the entire study period. Subjects who discontinued the study following required dose administration(s) but before completing may be replaced at the discretion of the sponsor and investigator. The replacement participant, where possible, should be Japanese, Chinese, or non-Japanese and non-Chinese to match the discontinued participant.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - consensus ethical principles derived from international guidelines including the Declaration of Helsinki (WMA 2013) and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - applicable ICH GCP guidelines, and
  - applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (for example, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures, and
  - providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 Code of Federal Regulations, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulations 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

10.1.3. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information, which would make the participant identifiable will not be transferred.
- The participant must be informed that his or her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for his/her data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The sponsor has processes in place to ensure data protection, information security, and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.1.4. Committees Structure

No data monitoring committee will be involved in this study.

10.1.5. Dissemination of Clinical Study Data

Communication of suspended or terminated dosing

If a decision is taken to suspend or terminate dosing in the trial due to safety findings, this decision will be communicated by Lilly to all investigators (for example, by phone and/or email) as soon as possible. It will be a requirement that investigators respond upon receipt to confirm that they understand the communication and have taken the appropriate action prior to further dosing any participants with study intervention. Any investigator not responding will be

followed up by Lilly personnel prior to any further planned dosing. If a dose is planned imminently, Lilly personnel will immediately, and continually, use all efforts to reach investigators until contact is made and instructions verified.

Reports

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete data set would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses (for example, trial not yet unblinded), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

Data

The sponsor does not proactively share data from Phase 1 clinical trials. Requests for access to Phase 1 clinical trial data are evaluated on a case-by-case basis taking into consideration the ability to anonymize the data and the nature of the data collected.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the sponsor or designee electronically (for example, laboratory data). The investigator is responsible for verifying that the data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Source data may include laboratory tests, medical records, and clinical notes.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality check of the data.
- The sponsor assumes accountability for actions delegated to other individuals (for example, contract research organizations).

- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP (EMA 2016), and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by sponsor or its representatives and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data capture system

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data capture system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided electronic data capture system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Data collected via the sponsor-provided data capture system(s) will be stored at third-party. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system(s). Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports or electronic transfers will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

Data from complaint forms submitted to sponsor will be encoded and stored in the global product complaint management system.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Section 10.1.6.

10.1.8. Study and Site Start and Closure

First act of recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

Study or site termination

The sponsor or sponsor's designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to

For study termination

- discontinuation of further study intervention development.

For site termination

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- inadequate recruitment (evaluated after a reasonable amount of time) of participants by the investigator, and
- total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.9. Publication Policy

In accordance with the sponsor's publication policy, the results of this study will be submitted for publication by a peer-reviewed journal if the results are deemed to be of significant medical importance.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in the table below will be performed by the central laboratory or local laboratory.
- In circumstances where the sponsor approves local laboratory testing in lieu of central laboratory testing (in the table below), the local laboratory must be qualified in accordance with applicable local regulations.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of the laboratory safety results.

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel.

Safety Laboratory Tests

Hematology	**Clinical Chemistry**
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate[i]
Mean cell volume	Chloride[i]
Mean cell hemoglobin	Calcium (total)
Mean cell hemoglobin concentration	Phosphorus/Phosphate[i]
Leukocytes (white blood cells [WBCs])	Glucose (fasting)
Platelets	Blood urea nitrogen (BUN)
Serum immunoglobulins (IgA, IgM, IgD, IgE and IgG)[h]	Creatinine
Differential WBC (absolute counts) of	Total protein
Neutrophils	Albumin
Lymphocytes	Total bilirubin
Monocytes	Alkaline phosphatase (ALP)
Eosinophils	Aspartate aminotransferase (AST)
Basophils	Alanine aminotransferase (ALT)
B Cells	Gamma-glutamyl transferase (GGT)[i]
T Cells	Beta D-glucan[g]
NK cells	
Urinalysis	
Specific gravity	
pH	**Fasting Lipid Panel**
Protein	Total cholesterol
Glucose	Triglycerides
Ketones	Low-density lipoprotein (LDL)
Bilirubin	High-density lipoprotein (HDL)
Urobilinogen	LDL/HDL ratio
Leukocytes	
Blood	
Nitrite	Hepatitis B surface antigen[a,d]
Microscopic examination of sediment[c]	Hepatitis B core antibody[a,d]
	Hepatitis B surface antibody[a,d] Hepatitis B DNA[d] Hepatitis C antibody[a,d]
Urine Drug Screen/Cotinine (nicotine)[b]	HIV[d]
Ethanol testing[b]	Pregnancy test (if applicable)[e]
Amphetamine Barbiturates Benzodiazepines Cocaine Cannabis Methylenedioxymethamphetamine (MDMA) Opiates Oxycodone Phencyclidine Tricyclic antidepressants	FSH (if applicable)[a]

Propoxyphene	
	Thyroid-stimulating hormone (optional)[f] Syphilis test[a]

Abbreviations: DNA = deoxyribonucleic acid; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; IgA = immunoglobulin A; IgD = immunoglobulin D; IgE = immunoglobulin E; IgG = immunoglobulin G; IgM = immunoglobulin M; RBC = red blood cell.

Note: Results of these assays will be validated by the local laboratory at the time of testing. Additional tests may be performed or auto calculated by the laboratory as part of its standard panel that cannot be removed. Some of the above parameters are calculated from measured values. Omission of calculated values will not be considered as a protocol violation.

[a] Performed at screening only.

[b] Urine drug screen and ethanol level may be repeated prior to admission to the clinical research unit and at other times indicated in the Schedule of Activities.

[c] Test only if dipstick result is abnormal.

[d] These tests may be waived if performed within 6 months prior to screening, and if test results are available for "review" for hepatitis B, C, and HIV.

[e] Serum pregnancy test at screening. Urine pregnancy test at all other time points. Performed on all female participants.

[f] To be performed on participants who are on thyroid medication or with a history of thyroid disease.

[g] Evaluation of beta-D-glucan at subsequent visits may be performed at a local laboratory.

[h] To be done centrally.

[i] To be done at the discretion of the clinical site.

10.2.1. Blood Sampling Summary

These tables summarize the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study.

Protocol J3V-MC-KKAA Sampling Summary
Part A

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	20.5	1	20.5
Clinical laboratory tests[a]	11.5	13	149.5
Immunoglobulins	5	7	35
Pharmacokinetics[b]	3	IV cohorts: 19 SC cohorts: 18	IV cohorts: 57 SC cohorts: 54
CCI			
CCI			
Blood discard for cannula patency	1	5	5
Blood samples for flow cytometry	2	10	20
Immunogenicity[b]	10	4	40
Pharmacogenetics	3	1	3
T-regulator proliferation	2	4	8
Total			IV cohorts: 418 SC cohorts: 415
Total for clinical purposes (rounded up to nearest 10 mL)			IV cohorts: 430 SC cohorts: 430

Abbreviations: IV = intravenous; SC = subcutaneous.

[a] Additional samples may be drawn if needed for safety purposes.
[b] Additional 3 samples may be drawn if required.

Part B (Cohort 1): CCI Dosing Schedule

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	20.5	1	20.5
Clinical laboratory tests[a]	11.5	18	207
Immunoglobulins	5	9	45
Pharmacokinetics[b]	3	IV cohorts: 28 SC cohorts: 26	IV cohorts: 84 SC cohorts: 78
CCI			
CCI			
Blood discard for cannula patency	1	5	5
Blood samples for flow cytometry	2	9	18
Immunogenicity[b]	10	5	50
Pharmacogenetics	3	1	3
T-regulator proliferation	2	4	8
Total			IV cohorts: 545.5 SC cohorts: 539.5
Total for clinical purposes (rounded up to nearest 10 mL)			IV cohorts: 550 SC cohorts: 550

Abbreviations: IV = intravenous; SC = subcutaneous.

[a] Additional samples may be drawn if needed for safety purposes.

[b] Additional 3 samples may be drawn if required.

Part B (Cohort 2): CCI Dosing Schedule

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	20.5	1	20.5
Clinical laboratory tests[a]	11.5	13	149.5
Immunoglobulins	5	6	30
Pharmacokinetics[b]	3	IV cohorts: 26 SC cohorts: 27	IV cohorts: 78 SC cohorts: 81
CCI			
CCI			
Blood discard for cannula patency	1	5	5
Blood samples for flow cytometry	2	10	20
Immunogenicity[b]	10	5	50
Pharmacogenetics	3	1	3
T-regulator proliferation	2	5	10
Total			IV cohorts: 486 SC cohorts: 501
Total for clinical purposes (rounded up to nearest 10 mL)			IV cohorts: 495 SC cohorts: 510

Abbreviations: IV = intravenous; SC = subcutaneous.

[a] Additional samples may be drawn if needed for safety purposes.

[b] Additional 3 samples may be drawn if required.

Part C: CCI [redacted] Dosing Schedule

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	14-17	1	17
Clinical laboratory tests[a]	8	10	80
Immunoglobulins	5	5	25
Pharmacokinetics[b]	3	IV cohorts: 19 SC cohorts: 15	IV cohorts: 57 SC cohorts: 45
CCI [redacted] CCI			
Blood discard for cannula patency	1	5	5
Blood samples for flow cytometry	2	6	12
Beta-D-glucan	2.5	1	2.5
Immunogenicity[b]	10	5	50
Pharmacogenetics	3	1	3
T-regulator proliferation	2	5	10
Total			IV cohorts: 352.5 SC cohorts: 340.5
Total for clinical purposes (rounded up to nearest 10 mL)			IV Cohorts: 360 SC cohorts: 350

Abbreviations: IV = intravenous; SC = subcutaneous.

[a] Additional samples may be drawn if needed for safety purposes.
[b] Additional 3 samples may be drawn if required.

Part C: CCI Dosing Schedule

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	14-17	1	17
Clinical laboratory tests[a]	8	12	96
Immunoglobulins	5	5	25
Pharmacokinetics[b]	3	IV cohorts: 24 SC cohorts: 20	IV cohorts: 72 SC cohorts: 60
CCI CCI			
Blood discard for cannula patency	1	5	5
Blood samples for flow cytometry	2	6	12
Beta-D-glucan	2.5	1	2.5
Immunogenicity[b]	10	5	50
Pharmacogenetics	3	1	3
T-regulator proliferation	2	5	10
Total			IV cohorts: 362.5 SC cohorts: 350.5
Total for clinical purposes (rounded up to nearest 10 mL)			IV Cohorts: 370 SC cohorts: 360

Abbreviations: IV = intravenous; SC = subcutaneous.

[a] Additional samples may be drawn if needed for safety purposes.
[b] Additional 3 samples may be drawn if required.

10.3. Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
1. An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. 2. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, and vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Medication error, misuse, or abuse of Investigational Medicinal Product, including signs, symptoms, or clinical sequelae. 1) Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
2) Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. 3) The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

4) Medical or surgical procedure (for example, endoscopy and appendectomy): the condition that leads to the procedure is the AE.
5) Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
6) Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:

Results in death

Is life-threatening

The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (for example, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect

- Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

Other situations

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Product Complaints

Product Complaint

- A PC is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also PCs:
  - Deficiencies in labeling information, and
  - Use errors for device or drug-device combination products due to ergonomic design elements of the product.
- PCs related to study interventions used in clinical trials are collected in order to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.
- Investigators will instruct participants to contact the site as soon as possible if he or she has a PC or problem with the study intervention so that the situation can be assessed.
- An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE.

10.3.4. Recording and Follow-up of AE and/or SAE and Product Complaints

AE, SAE, and Product Complaint Recording

- When an AE/SAE/PC occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/PC information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page and PC information is reported on the PC form.

Note: An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to sponsor or designee in lieu of completion of the CRF page for AE/SAE and the PC form for PCs.
- There may be instances when copies of medical records for certain cases are requested by sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship/
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB in their assessment.

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to sponsor or designee.
- The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide sponsor or designee with a copy of any post-mortem findings including histopathology.

10.3.5. Reporting of SAEs

SAE Reporting via SAE Report

- Facsimile transmission of the SAE Report is the preferred method to transmit this information to the sponsor or designee.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE Report within the designated reporting time frames.
- Contacts for SAE reporting can be found in the SAE Report.

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

- An investigator who receives an investigator safety report describing a SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Word/Phrase	Definition
Women of childbearing potential	Females are considered a woman of childbearing potential if • they have had at least 1 cycle of menses, or • they have Tanner 4 breast development. Any amount of spotting should be considered menarche. If Tanner staging of breasts is performed as part of study procedures, please refer to the Reproductive, Pregnancy and Pediatrics Safety Committee Safety Guidance for Children in Clinical Trial regarding Tanner staging.
Women not of childbearing potential	Females are considered women not of childbearing potential if • they have a congenital anomaly such as Mullerian agenesis, • they are infertile due to surgical sterilization, or • they are postmenopausal. Examples of surgical sterilization include hysterectomy, bilateral oophorectomy, and tubal ligation.
Postmenopausal state	The postmenopausal state should be defined as 1. a woman at any age at least 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note, or 2. a woman at least 40 years of age and up to 55 years old with an intact uterus, not on hormone therapy*, who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND With a follicle-stimulating hormone >40 mIU/mL; or 3. a woman 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or 4. a woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy. * Women should not be taking medications during amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormone, antiestrogens, selective estrogen receptor modulators (SERMs), or chemotherapy that could induce transient amenorrhea.
Reproductive toxicology studies	Embryofetal studies are toxicity studies in pregnant animals designed to identify abnormalities in the development of fetuses, which could indicate potential for teratogenicity in humans. The relevant dosing period is during organogenesis.

10.4.2. Contraception Guidance

For male participants

Topic	Guidance
Contraception for men receiving a genotoxic drug and have a female partner of childbearing potential	• Agree to remain abstinent (if this is their preferred and usual lifestyle), or • use 1 additional effective method of contraception

The table below describes contraception guidance for all men.

Topic	Guidance
For all men	• Should refrain from sperm donation for the duration of the study
Contraception for men with partners of childbearing potential	• Either remain abstinent (if this is their preferred and usual lifestyle), or • must use condoms during intercourse for the duration of the study
Contraception for men in exclusively same sex relationships as their preferred and usual lifestyle	• Are not required to use contraception

For female participants

WOCBP who are completely abstinent as their preferred and usual lifestyle, or in a same sex relationship, as part of their preferred and usual lifestyle

Must…	Must not…
agree to either remain abstinent, or	• use periodic abstinence methods o calendar o ovulation o symptothermal, or o post-ovulation • declare abstinence just for the duration of a trial
stay in a same sex relationship without sexual relationships with males	• use the withdrawal method

WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or in a same sex relationship, as part of their preferred and usual lifestyle

Topic	Explanation
Pregnancy testing	Negative urine result at screening followed by a negative serum result within 24 hours prior to treatment exposure.
	Note: Subsequent pregnancy testing is compound specific.
Contraception	Agree to use 2 forms of effective contraception, where at least 1 form must be highly effective (less than 1% failure rate).

For WOCBP: Abstinence or 2 effective forms of contraception is to be maintained

- for 5 half-lives following the last dose or
- until the serum drug concentration is below the pharmacologic effect level,
- whichever is longer.

Examples of highly effective, effective, and unacceptable methods of contraception can be found below for all participants:

Methods	Examples
Highly effective contraception	• combination oral contraceptive pill and mini-pill* • implanted contraceptives* • injectable contraceptives* • contraceptive patch* (only women <198 pounds or 90 kg) • total abstinence • vasectomy (if only sexual partner) • fallopian tube implants* (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring*, or • intrauterine devices
Effective contraception	• male or female condoms with spermicide* • diaphragms with spermicide or cervical sponges* • barrier method with use of a spermicide o condom with spermicide o diaphragm with spermicide*, or o female condom with spermicide* Note: The barrier method must include use of a spermicide (that is, condom with spermicide, diaphragm with spermicide, and female condom with spermicide) to be considered effective.
Ineffective forms of contraception	• spermicide alone • immunocontraceptives • periodic abstinence • fertility awareness (calendar method, temperature method, combination of above 2, cervical mucus, and symptothermal) • withdrawal • post coital douche, and • lactational amenorrhea

* Not available in Japan.

10.5. Appendix 5: Genetics

Use/analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.

- DNA samples will be used for research related to LY3844583 or autoimmune and inflammatory disorders and related diseases. They may also be used to develop tests/assays including diagnostic tests related to LY3844583 and/or interventions of this drug class and autoimmune and inflammatory disorders. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- Analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to LY3844583 or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the blood and/or DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on LY3844583 or study interventions of this class or indication continues but no longer than 15 years or other period as per local requirements.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments and Study Intervention Restart/Rechallenge Guidelines

10.6.1. Hepatic Monitoring and Abnormal Hepatic Biochemical Tests

Close hepatic monitoring

Laboratory tests including ALT, AST, ALP, TBL, D. Bil, gamma-glutamyl transferase, and CK, should be repeated within 48 to 72 hours to confirm the abnormality and to determine whether it is increasing or decreasing if 1 or more of these following conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN
ALP <1.5x ULN	ALP ≥2x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for patients with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥1.5x baseline (except for patients with Gilbert's syndrome)

Abbreviations: ALP = alkaline phosphatase, ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin level; ULN = upper limit of normal

If the abnormality persists or worsens, clinical and laboratory monitoring and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, and history of alcohol drinking and other substance abuse.

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks if the participant's clinical condition and lab results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive hepatic evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if 1 or more of these following conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ⩾3x ULN with hepatic signs/symptoms[a] or ALT or AST ⩾5x ULN
ALP <1.5x ULN	ALP ⩾3x ULN
TBL <1.5x ULN	TBL ⩾2x ULN (except for patients with Gilbert's syndrome)
ALT or AST ⩾1.5x ULN	ALT or AST ⩾2x baseline with hepatic signs/symptoms[a], or ALT or AST ⩾3x baseline
ALP ⩾1.5x ULN	ALP ⩾2x baseline
TBL ⩾1.5x ULN	TBL ⩾2x baseline (except for patients with Gilbert's syndrome)

Abbreviations: ALP = alkaline phosphatase, ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin level; ULN = upper limit of normal

[a] Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin time-international normalized ratio; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or computed tomography scan).

Based on the patient's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.

Additional hepatic data collection (hepatic safety CRF) in study participants who have abnormal liver tests during the study

Additional hepatic safety data collection in hepatic safety CRF should be performed in study participants who meet 1 or more of the following 5 conditions:

1. Elevation of serum ALT to ≥5x ULN on 2 or more consecutive blood tests (if baseline ALT <1.5x ULN)
   - In participants with baseline ALT ≥1.5x ULN, the threshold is ALT ≥3x baseline on 2 or more consecutive tests
2. Elevated TBL to ≥ 2x ULN (if baseline TBL <1.5x ULN) (except for cases of known Gilbert's syndrome)
   - In participants with baseline TBL ≥1.5x ULN, the threshold should be TBL ≥2x baseline
3. Elevation of serum ALP to ≥2x ULN on 2 or more consecutive blood tests (if baseline ALP <1.5x ULN)
   - In participants with baseline ALP ≥1.5x ULN, the threshold is ALP ≥2x baseline on 2 or more consecutive blood tests

4. Hepatic event considered to be an SAE.
5. Discontinuation of study drug due to a hepatic event.

Note: The interval between the 2 consecutive blood tests should be at least 2 days.

Hepatic evaluation testing

The Lilly-designated central laboratory must complete the analysis of all selected testing except for microbiology testing.

Local testing may be performed in addition to central testing when necessary for immediate participant management.

Results will be reported if a validated test or calculation is available.

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
	Copper
Coagulation	Ethyl alcohol (EtOH)
Prothrombin time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin A (IgA) (quantitative)
Hepatitis A virus (HAV) testing:	Immunoglobulin G (IgG) (quantitative)
HAV total antibody	Immunoglobulin M (IgM) (quantitative)
HAV IgM antibody	Phosphatidylethanol (PEth)
Hepatitis B virus (HBV) testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Antinuclear antibody (ANA)

Hematology	**Clinical Chemistry**
Hepatitis B core IgG antibody	Antismooth muscle antibody (ASMA)[a]
HBV DNA[b]	Antiactin antibody[c]
Hepatis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA[b]	EBV DNA[b]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA[b]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA[b]	HSV (Type 1 and 2) DNA[b]
Microbiology[d]	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

Abbreviations: DNA = deoxyribonucleic acid; INR = international normalized ratio; RNA = ribonucleic acid.

[a] Not required if antiactin antibody is tested.

[b] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

[c] Not required if antismooth muscle antibody (ASMA) is tested.

[d] Assayed ONLY by investigator-designated local laboratory; no central testing available.

10.7. Appendix 7: Abbreviations and Definition

Term	Definition
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence.
ADA	antidrug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AtD	atopic dermatitis
AUC	area under the concentration versus time curve
blinding/masking	A single-blind study is one in which the investigator and/or the investigator's staff are aware of the treatment but the participant is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/the investigator's staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
CD3	cluster of differentiation 3
CIOMS	Council for International Organizations of Medical Sciences
clinical research physician	Individual responsible for the medical conduct of the study. Responsibilities of the clinical research physician may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
C_{max}	maximum observed drug concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant.
CRS	cytokine release syndrome
CRU	clinical research unit

Term	Definition
Data monitoring committee	A data monitoring committee or data monitoring board (DMB) is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention and to make recommendations to the sponsor regarding the stopping of a study for efficacy, or for harms, or for futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.
DLQI	Dermatology Life Quality Index
DNA	deoxyribonucleic acid
EASI	Eczema Area and Severity Index
ECG	electrocardiogram
eCRF	electronic case report form
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	Ethical Review Board
F	bioavailability
Fab	fragment antigen-binding
FcγR	Fc gamma receptor
GCP	good clinical practice
GITR	glucocorticoid-induced tumor necrosis factor receptor
GITRL	glucocorticoid-induced tumor necrosis factor receptor-related protein ligand
HBc	hepatitis B core
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HC	heavy chain
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IAD	interim access to data
IB	Investigator's Brochure

Term	Definition
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product (see also "investigational product") A medicinal product, which is being tested or used as a reference, including as a placebo, in a clinical trial.
informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
IP	investigational product; a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. See also "IMP."
IRB	Institutional Review Board
IRR	infusion-related reaction
ISR	injection-site reaction
IV	intravenous
K_D	equilibrium dissociation constant
KKAA	Study J3V-MC-KKAA
mAb	monoclonal antibody
MAD	multiple-ascending dose
mBOCF	modified baseline observation carried forward

Term	Definition
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold 1 or more of the 5 “rights” of medication use: the right participant, the right drug, the right dose, right route, and at the right time. In addition to the core 5 rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, and protocol), or • shared use of cartridges, prefilled pens, or both.
misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
mITT	modified intent-to-treat
NK	natural killer
NOAEL	no-observed-adverse-effect level
NRI	nonresponder imputation
NRS	numeric rating scale
participant	equivalent to Clinical Data Interchange Standards Consortium term “subject”: an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control.
PC	product complaint
PK/PD	pharmacokinetics/pharmacodynamics
POEM	Patient-Oriented Eczema Measure
PR	pulse rate
CCI	[redacted]
CCI	[redacted]
QTcF	Fredericia’s corrected QT interval
RNA	ribonucleic acid
CCI	[redacted]

Term	Definition
SAD	single-ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCORAD	SCORing Atopic Dermatitis
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SoA	Schedule of Activities
SRC	Safety Review Committee
TB	tuberculosis
TBL	total bilirubin
TCNI	topical calcineurin inhibitor
TCS	topical corticosteroid
TE-ADA	treatment-emergent antidrug antibody
TE-ADA+	treatment-emergent antidrug antibody positive
TEAE	treatment-emergent adverse event
TNFRSF18	tumor necrosis factor receptor superfamily 18
TRAF2	TNF receptor-associated factor 2
TRAF5	TNF receptor-associated factor 5
Treg	regulatory T cell
ULN	upper limit of normal
VHH	variable region of the heavy chain of a heavy chain only antibody
vIGA-AD	Validated Investigator's Global Assessment for Atopic Dermatitis
V_{max}	maximum velocity of the elimination
WBC	white blood cell
WOCBP	women of childbearing potential

10.8. Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment c: 12 May 2023

Overall Rationale for the Amendment:

This protocol has been amended to increase the number of enrolled patients with atopic dermatitis in Part C to account for possible dropouts and to help ensure [redacted] completers.

Minor editorial changes have also been done and are not presented in the summary of changes table.

Section # and Name	Description of Change	Brief Rationale
Section 1.1: Synopsis	Updated the total number of enrolled participants from approximately [redacted] to approximately [redacted] Updated the total number of evaluable participants from approximately [redacted] to approximately [redacted] Updated the number of patients enrolled in Part C from [redacted] to [redacted]	An additional [redacted] participants were added to Part C to account for possible dropouts. This increases the total number of enrolled and evaluable participants.
[redacted]	[redacted]	[redacted]
Section 4.1: Overall Design	Updated the number of patients with atopic dermatitis in Part C from [redacted] to [redacted] Updated the number of patients to receive LY3844583 from [redacted] to [redacted] and updated the number of patients to receive placebo from [redacted] to [redacted] Updated the ratio for Repeat-dose Part C in Table KKAA.1 from [redacted] LY: [redacted] PBO to [redacted] LY: [redacted] PBO	An additional [redacted] participants were added to Part C to account for possible dropouts. This increases the total number of enrolled and evaluable participants and the number of patients with atopic dermatitis.
Section 9.5: Sample Size Determination	Updated the total number of enrolled participants from at least [redacted] to approximately [redacted] Clarified that sample sizes for Parts A and B are not adjusted for	An additional [redacted] participants were added to Part C to account for possible dropouts. This increases the total number of enrolled and evaluable participants.

Section # and Name	Description of Change	Brief Rationale
	potential dropouts and that the samples size for Part C is adjusted to account for potential dropouts. Removed text stating that replacement participants should be assigned to the same treatment arm as the discontinued participant.	Replacement participants for dropouts should be randomized independently of the treatment assignment of the discontinued participant to maintain balance in measured and unmeasured risk-factors.

Amendment b: 09 February 2023

Overall Rationale for the Amendment:

This protocol has been amended to make modifications to aspects of the study design in Part C (patients with atopic dermatitis) in order to adhere to certain requirements in Japan, including the inclusion criteria, the exclusion criteria, blood sampling summary, and contraception guidance.

Additional changes have been made to fix errors from the previous protocol. These changes are presented in the summary of changes table.

Minor editorial changes have also been done and are not presented in the summary of changes table.

Section # and Name	Description of Change	Brief Rationale
Section 1.3.2.1: Part B: Cohort 1 – CCI [redacted] Dosing Schedule	Added Note to state that missed CCI [redacted] sample collection will not be considered a protocol deviation Updated footnote m to specify that IgA, IgM, IgD, IgE, and IgG assessments can be performed centrally or locally in the event of a delay from central testing	Corrected previous errors
Section 1.3.2.2: Part B: Cohort 2 – CCI [redacted] Dosing Schedule	Changed the last Visit Number from V16 to V18 Added Note to state that missed CCI [redacted] sample collection will not be considered a protocol deviation Updated footnote m to specify that IgA, IgM, IgD, IgE, and IgG assessments can be performed centrally or locally in the event of a delay from central testing	Corrected previous errors

Section # and Name	Description of Change	Brief Rationale
Section 1.3.3.1: Part C: CCI [redacted] Dosing Schedule	Added Electrocardiogram testing to Visit 14 and Early Discontinuation visit Added collection of CCI [redacted] to Early Discontinuation visit	Corrected previous errors
Section 1.3.3.2: Part C: CCI [redacted] Dosing Schedule	Added collection of CCI [redacted] at Predose to Visit 4 Added collection of CCI [redacted] at Predose to Visit 4	Corrected previous errors
Section 4.3: Justification for Dose	Changed footnote g in Table KKAA.2 from AUC0-∞ (CCI [redacted] µg•hr/mL) to AUC0-∞ (CCI [redacted] µg•hr/mL)	Corrected previous error
Section 5.1.1: Additional Inclusion Criteria for Part C (Patients with AtD)	Deleted "pimecrolimus" from the example medication listed in [13a]	Corrected as the medication not permitted in Japan
Section 5.2.1: Additional Exclusion Criteria for Part C (Patients with AtD)	Added Criterion [48] to exclude women who are lactating Added Criterion [49] to exclude patients who have experienced hypersensitivity to the active substance or to any of the excipients Added Criterion [50] along with definitions to exclude patients who have evidence of, or a positive test for, HBV infection	Added as the requirements for Part C in Japan
Section 5.3.1.1: Meals and Dietary Restrictions for Part C	Added section to clarify that participants in Part C are required to fast for approximately 10 hours before visits that include clinical chemistry testing	Added as the requirement for Part C in Japan
Section 10.2.1: Blood Sampling Summary	Added Blood samples for flow cytometry in Part C: CCI [redacted] Dosing Schedule Changed the Number of Blood Samples for Immunogenicity from 8 to 5 in Part C: CCI [redacted] Dosing Schedule	Corrected previous errors

Section # and Name	Description of Change	Brief Rationale
	Changed the Total Volume for Immunogenicity from 80 mL to 50 mL in Part C: CCI Dosing Schedule Changed the Number of Blood Samples for T-regulator proliferation from 4 to 5 in Part C: CCI Dosing Schedule Changed the Total Volume for T-regulator proliferation from 8 mL to 10 mL in Part C: CCI Dosing Schedule Changed the Total Volume in IV cohorts from 368.5 mL to 352.5 mL and changed SC cohorts from 356.5 mL to 340.5 mL in Part C: CCI Dosing Schedule Changed the Total Volume for clinical purposes in IV cohorts from 375 mL to 360 mL and changed SC cohorts from 365 mL to 350 mL in Part C: CCI Dosing Schedule Added Blood samples for flow cytometry in Part C: CCI Dosing Schedule Changed Total Volume in IV cohorts from 350.5 mL to 362.5 mL and changed SC cohorts from 338.5 mL to 350.5 mL in Part C: CCI Dosing Schedule Changed the Total Volume for clinical purposes in IV cohorts from 360 mL to 370 mL and changed SC cohorts from 345 mL to 360 mL in Part C: CCI Dosing Schedule	

Section # and Name	Description of Change	Brief Rationale
Section 10.4.2: Contraception Guidance	Changed plasma concentration to serum concentration for Women of Child Bearing Potential who are not completely abstinent as their preferred and usual lifestyle Added a footnote and * next to the examples of contraception that are not available in Japan	Corrected previous error Clarified the contraceptive methods not permitted in Japan

Amendment a: 23 January 2023

Overall Rationale for the Amendment:

This protocol has been amended to update the overall study design throughout the entire protocol to include the option of evaluating safety, tolerability, PK of LY3844583 in healthy participants and participants with AtD with CCI dosing for Part B multiple-ascending dose Cohort 2 and in Part C.

Minor editorial changes have also been done and are not presented in the summary of changes table.

Section # and Name	Description of Change	Brief Rationale
Section 1.1: Synopsis	Updated the total number of doses from up to CCI doses to up to CCI doses in Part B Updated the dosing interval from CCI in Part B Updated the total number of doses from CCI doses to up to CCI doses in Part C Updated the dosing interval from CCI in Part C Updated the text to make distinction between multiple ascending dose (MAD) Part B CCI Cohort 1 intravenous (IV) dosing on Days CCI and MAD Part B CCI Cohort 2 IV or subcutaneous (SC) dosing on Days CCI	All changes in this section are made to allow CCI dosing schedules in Parts B and C

Section # and Name	Description of Change	Brief Rationale
	Updated the text to account for the alternate CCI dosing, in addition to CCI , in Part C	
CCI [redacted]	[redacted]	[redacted]
Section 1.3.1: Part A: Single-Ascending Dose in Healthy Participants	Added an ECG assessment on Day [redacted] in the Schedule of Activities (SoA)	Corrected previous error
Section 1.3.2.1: Part B: Cohort 1 – CCI Dosing Schedule	Removed Subcutaneous local injection site assessment from screening visit in the SoA Update footnote n to include textual reference for further details on injection-site assessments	Corrected previous errors
Section 1.3.2.2: Part B: Cohort 2 – CCI Dosing Schedule	Created new CCI dosing SoA for Part B, Cohort 2	Changes made to allow CCI dosing schedule in Parts B
Section 1.3.3.1: Part C: CCI Dosing Schedule	Updated footnote j to specify that IgA, IgM, IgD, IgE, and IgG assessments can be performed centrally or locally in the event of a delay from central testing	Corrected previous error
Section 1.3.3.2: CCI Dosing Schedule	Created new CCI dosing SoA for Part C	Changes made to allow CCI dosing schedules in Part C
Section 4.1: Overall Design	Updated text to clarify that MAD Part B Cohort 1 will receive IV dose CCI on Days CCI Updated text to clarify that MAD Part B Cohort 2 will receive IV or SC dose CCI on Days CCI [redacted] Updated text to clarify that Part C will receive CCI SC or IV dose	All changes in this section made to allow CCI dosing schedules in Parts B and C

Section # and Name	Description of Change	Brief Rationale
Section 4.3: Justification for Dose	Updated Table KKAA.2 to provide predicted margin of safety with MAD highest dose of CCI mg SC and IV CCI Updated text and Table KKAA.3 to include prediction for blood and CCI at Day [redacted] Updated text and Table KKAA.4 to include prediction for blood and tissue CCI data at Day [redacted] Updated text to clarify that dosing in MAD Part B Cohort 1 will be CCI mg IV CCI on Days CCI [redacted] Added text to specify that dosing in MAD Part B Cohort 2 is planned as ≤CCI mg CCI IV or SC on Days CCI and route of administration will be based on emerging data from SAD and MAD Cohort 1. Updated text to clarify that Part C will be CCI or CCI [redacted], and that IV or SC route of administration will be decided based on emerging data from SAD Part A and MAD Part B cohorts. Added text to include CCI d to a repeated dose of CCI mg CCI for margin of safety	All changes in this section made to allow CCI dosing schedules in Parts B and C
Section 5.1.1: Additional Inclusion Criteria for Part C (Participants with AtD)	Removed statement from Inclusion Criterion #16 as it was a repeat statement from Inclusion Criterion #15	Corrected previous error
Section 6.3: Measures to Minimize Bias: Randomization and Blinding	Updated the text to state that blinding will be maintained throughout the conduct of the study as described in the Statistical Analysis Plan as opposed to in the separate Blinding Plan.	Corrected previous error

Section # and Name	Description of Change	Brief Rationale
Section 6.5: Dose Modification	Removed statement that details will be included in the SRC Charter.	Corrected previous error
Section 10.2.1: Blood Sampling Summary	Updated to clarify blood sampling summary table for Part B (Cohort 1) CCI Dosing Schedule Added new blood sampling summary table for Part B (Cohort 2) CCI Dosing Schedule Updated to clarify blood sampling summary table for Part C CCI Dosing Schedule Added new blood sampling summary table for Part C CCI Dosing Schedule	All changes in this section made to allow CCI dosing schedules in Parts B and C

11. References

Dong JQ, Salinger DH, Endres CJ, et al. Quantitative prediction of human pharmacokinetics for monoclonal antibodies: retrospective analysis of monkey as a single species for first-in-human prediction. *Clin Pharmacokinet*. 2011;50(2):131-142. https://doi.org/10.2165/11537430-000000000-00000

Eichenfield LF, Tom WL, Chamlin SL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol.* 2014:70(2):338-351. https://doi.org/10.1016/j.jaad.2013.10.010

[EMA] European Medicines Agency. Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products. Published July 20, 2017. Accessed February 07, 2022. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational_en.pdf

[EMA] European Medicines Agency. Guideline for good clinical practice E6(R2). EMA/CHMP/ICH/135/1995. Published December 01, 2016. Accessed February 15, 2022. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf

Gallagher D, Heymsfield SB, Heo M, et al. Healthy percentage body fat ranges: an approach for developing guidelines based on body mass index. *Am J Clin Nutr*. 2000;72(3):694-701. https://doi.org/10.1093/ajcn/72.3.694

Kimball AB, Naegeli AN, Edson-Heredia E, et al. Psychometric properties of the Itch Numeric Rating Scale in patients with moderate-to-severe plaque psoriasis. *Br J Dermatol*. 2016;175(1):157-162. https://doi.org/10.1111/bjd.14464

Leach MW, Clarke DO, Dudal S, et al. Strategies and recommendations for using a data-driven and risk-based approach in the selection of first-in-human starting dose: an international consortium for innovation and quality in pharmaceutical development (IQ) assessment. *Clin Pharmacol Ther*. 2021;109(6):1395-1415. https://doi.org/10.1002/cpt.2009

Naegeli AN, Flood E, Tucker J, et al. The Worst Itch Numeric Rating Scale for patients with moderate to severe plaque psoriasis or psoriatic arthritis. *Int J Dermatol*. 2015 Jun;54(6):715-22. https://doi.org/10.1111/ijd.12645

Okamoto N, Hoson A, Shibata K, et al. Accuracy of self-reported height, weight and waist circumference in a Japanese sample. *Obes Sci Pract*. 2017;3(4):417-424. https://doi.org/10.1002/osp4.122

[PSEHB/ELD] Pharmaceutical Safety and Environmental Health Bureau/Evaluation and Licensing Division. Notification No. 1225/1. Revision of the guidance for establishing safety in first-in-human studies during drug development. 2019. Available at: https://www.mhlw.go.jp/hourei/doc/tsuchi/T191227I0050.pdf. Accessed February 07, 2022.

Ryman JT, Meibohm B. Pharmacokinetics of monoclonal antibodies. *CPT Pharmacometrics Syst Pharmacol*. 2017;6(9):576-588. https://doi.org/10.1002/psp4.12224

Shah DK, Betts AM. Antibody biodistribution coefficients: inferring tissue concentrations of monoclonal antibodies based on the plasma concentrations in several preclinical species and human. *MAbs*. 2013;5(2):297-305. https://doi.org/10.4161/mabs.23684

Smith BP, Vandenhende FR, DeSante KA, et al. Confidence interval criteria for assessment of dose proportionality. *Pharm Res*. 2000;17(10):1278-1283. https://doi.org/10.1023/a:1026451721686

Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. *J Clin Nurs*. 2005;14(7):798-804. https://doi.org/10.1111/j.1365-2702.2005.01121

Winthrop KL, Novosad SA, Baddley JW, et al. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. *Ann Rheum Dis.* 2015;74(12):2107-2116. https://doi.org/10.1136/annrheumdis-2015-207841

[WMA] World Medical Association. Declaration of Helsinki – Ethical principles for medical research involving human subjects. 64th WMA General Assembly, Fortaleza, Brazil. 2013. Available at: https://e-dmj.org/file/WMA-Declaration_of_Helsinki-2013.pdf. Accessed February 07, 2022.

Zou H, Zhu X, Zhang J, et al. Reference equations for the six-minute walk distance in the healthy Chinese population aged 18–59 years. *PloS One*. 2017;12(9):e0184669. https://doi.org/10.1371/journal.pone.0184669

Signature Page for VV-CLIN-118939 v1.0

Approval	PPD Medical Director 08-Jun-2023 20:31:40 GMT+0000

Approval	PPD Statistician 08-Jun-2023 20:35:19 GMT+0000

Signature Page for VV-CLIN-118939 v1.0